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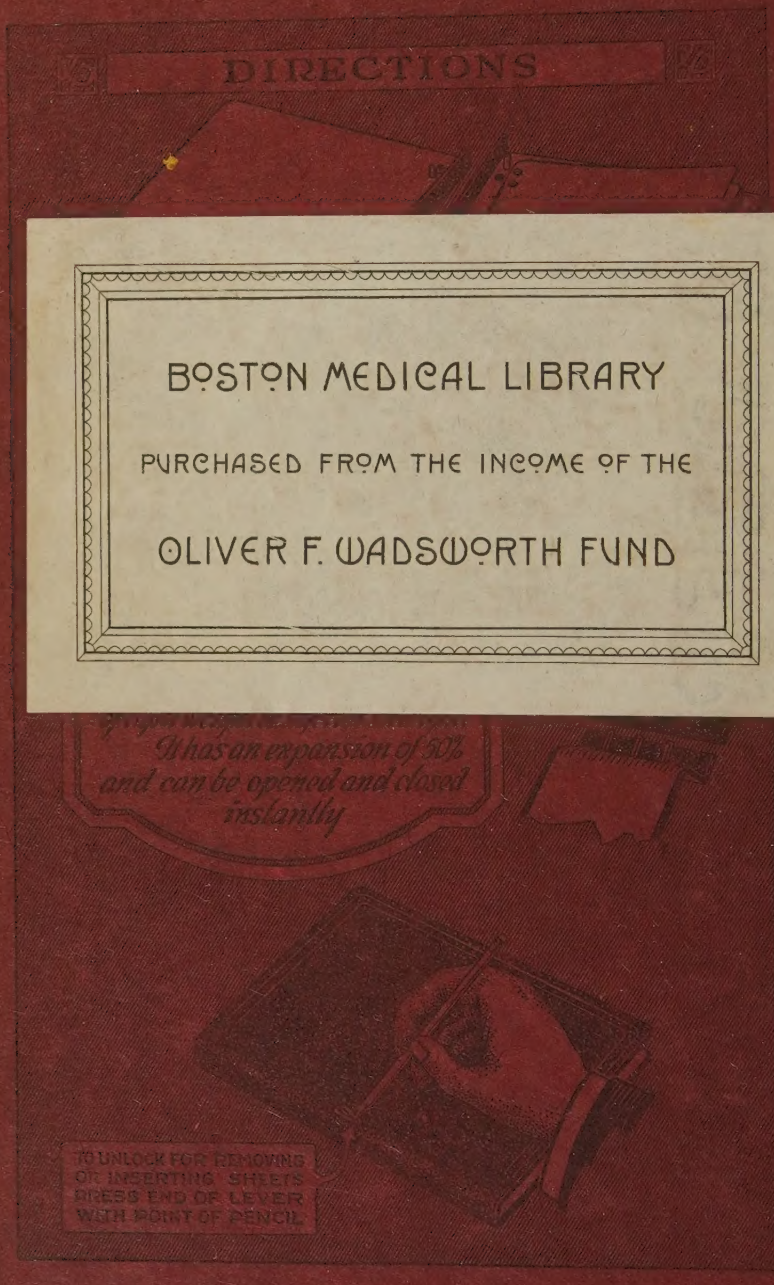

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MONOGRAPHS ON
DIAGNOSIS AND TREATMENT

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VOLUME IV

The Diagnosis and Treatment of

DISEASES OF

THE THYROID

By

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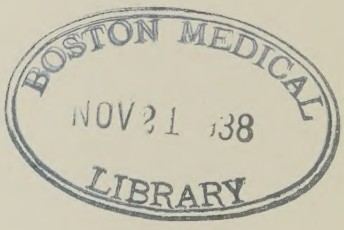

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FOREWORD

To the man who practices medicine two questions arise with great frequency; what is the matter with my patient, and how shall I treat his ills? To answer these questions correctly is to practice medicine in a satisfactory manner. Consequently, diagnosis and treatment are of vital interest to every physician.

In the modern era of medicine very striking advances have been made in methods of diagnosis. Many new methods of precision have become available for bedside use. Discoveries in physics and chemistry have been applied in the clinic. Laboratory methods have been simplified so that they are available in diagnosis; many of them are such that they can be carried out readily by the physician himself. Older methods of examining the patient have been improved, and the implication of many signs long known are better understood. In utilizing these methods, even more than ever, is there need for clinical knowledge and judgment based on experience. The good diagnostician of today must know more facts, understand the use of more methods than was true of former generations of medical men.

For a time in recent progress in medicine it seemed as if advance in methods of treatment lagged behind advance in methods of diagnosis. There was a period of therapeutic nihilism. Many old methods of treatment had been discarded as better knowledge indicated their futility, and their place was not taken at once by more effective measures. In a period in which pathological anatomy dominated medicine, and particularly a post-mortem pathological anatomy, effectively to treat

many diseases seemed an impossibility. This period was followed by a newer pathology based more on a study of the living with advance in knowledge of function. Concepts of abnormal function stimulated renewed interest in methods of treatment. Great advances in our knowledge of etiology again brought improved methods of treatment along the lines of immunization, antitoxic sera, etc. Chemists developed a chemotherapy. Many new measures of applying physical methods in treatment were developed. A more rational basis for psychotherapy was evolved. From all of these changes there has come a present period of medicine in which treatment in all of its forms occupies possibly a larger place in medical literature than any other phase of medicine.

With so much known of diagnosis and treatment and with so many things being steadily added by medical investigators, there is a real need among those who practice medicine for comprehensive discussions of diagnosis and treatment by men competent to select what is best and to present it with sufficient detail and clarity for it to be of practical help in the problems of practice. For this purpose this series of "Monographs on Diagnosis and Treatment" has been prepared. Each volume is a discussion of the diagnosis and treatment of a certain group of diseases. The series is to be issued in form to make possible revisions and additions as new knowledge is available. It is offered with the hope that they, who read it, will be prepared to render to their patients a better service.

HENRY A. CHRISTIAN, *Editor.*

PETER BENT BRIGHAM HOSPITAL
Boston, Mass., Oct. 1, 1938

PREFACE

The thyroid body, perhaps because of the high visibility it possesses when enlarged, has intrigued the mind of both physician and layman since antiquity. The literature on this organ consequently is enormous. The object of the present work is to provide for the practitioner a convenient handbook of not too great size containing the current views regarding the nature of the various disorders of the gland in question and the ways of recognizing them, together with a concise account of the more generally accepted present day methods of treatment. No attempt has been made to explore the literature completely. Reference will be made merely to the classical papers of the past and to the most pertinent ones of the present day. The work is based rather upon personal experience in handling these cases over a period of twenty-three years. Illustrative cases from the writers' experience will be used freely. A few of these are taken from private practice, but the great majority are from the Thyroid Clinic of the Massachusetts General Hospital, and the writers are deeply indebted to a group of colleagues whose labors they have drawn upon freely and whose opinions they have frequently appropriated. This Thyroid Clinic from the beginning has been a joint enterprise of the Medical, Surgical and Roentgenological Departments of the Hospital. It has been conducted with a view to combining the care of patients with study of their disease. It has been holding meetings formally since 1920 and a metabolism laboratory has been in operation since 1913. The number of cases coming under observation is by no means large as compared with those examined in

private clinics that specialize in thyroid disease, being, in a twenty-three year period, over sixteen hundred cases of toxic goitre, over four hundred cases of myxœdema and somewhat over twenty-two hundred cases of other thyroid diseases. It is, however, quite as large relatively as the total size of our institution warrants. Since it is a general teaching hospital one type of case cannot be taken to the exclusion of others. What we have done, and what many other clinics cannot do, is to study our patients carefully over a long period of time, thus getting a clear idea of the natural trend of their disease and the end results of treatment. Some cases have been under observation since 1913.

Particular acknowledgement is due to the late Dr. C. A. Porter, who has done much of the surgery, Dr. G. W. Holmes, who has done the roentgenography and roentgenotherapy, and to a series of research fellows who have conducted the metabolism work and made the clinical and laboratory investigations, Drs. J. C. Aub, W. G. Lennox, A. L. Barach, H. N. Segall, M. P. Starr, D. L. Sisco, C. I. Krantz, W. O. and P. K. Thompson, J. Lerman and S. Hertz. The writers are especially indebted to Dr. Phebe K. Thompson for aid in the collection and arrangement of the data for the present work.

For sake of convenience in comparing with other publications from this clinic, the illustrative cases are referred to by their Massachusetts General Hospital Metabolism Laboratory numbers.

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DISEASES OF THE THYROID

CHAPTER I

INTRODUCTORY

DEVELOPMENT OF OUR KNOWLEDGE OF THE THYROID

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For a proper understanding of the diseases of the thyroid some acquaintance with the normal structure and function of that organ is necessary. For the purpose of the present work on the diagnosis and treatment of thyroid disorders it has seemed to the writers that the historical method of attack may prove less boring to the clinician than the customary progression in separate sections through the embryology, anatomy, physiology, biochemistry, etc., of the organ in question. An attempt will be made, therefore, before diagnosis and treatment are discussed, to outline the development of our present knowledge of the thyroid as an endocrine gland in its more important features, without, of course, any pretense of covering completely so vast a subject. There is, perhaps, some merit in the method of forming a modern conception of a scientific subject by following the pathways blazed by the masters of the past.

Pre-Modern Period

The Greek and Roman writers made many references to goitre. Pliny wrote that none need be surprised at goitre in the Alps, so the Swiss endemic disease was quite familiar even then. But beyond this there is nothing that need detain us in the ancient literature.

In the Renaissance we have descriptions by Vesalius[1] (1543), Eustachius[2] (1552), and by William Wharton[3]. The last, in a work entitled, "Adenographia", published in London in 1656, is singularly illuminating. Wharton gave an excellent description of the location, size and weight of this gland, and furthermore bestowed upon it the name we know it by — thyroid, from the Greek Θυρεός, shield and εἶδος, like.

Wharton recognized a number of the important characteristics. For example, he noted that the gland is firmer and at the same time both more blood red in color and viscid than other glands. It is obvious that he clearly perceived that the thyroid has a very rich blood supply, and his speculations on its function are far advanced for his day. Its chief use, he believed, was to receive via the recurrent nerves certain superfluous humors, and to conduct them anew via the lymphatics into the veins. He also had, what may seem strange, ideas that the thyroid, by the heat from its rich blood supply, warmed up the colder cartilages to which it is attached, that it lubricated the larynx by its vapors, thus rendering the voice smoother and more melodious, and finally that it served to enhance the beauty of the neck by smoothing its contours, especially in women. The last may well be true, although we should hardly describe it nowadays as a function. The first, however, though quaintly incorrect, is at least prophetic in that it gives the idea

that this gland contributes some substance to the circulating blood.

The germ of this theory of internal secretion was apparently present in the eighteenth century in the mind of Théophile de Bordeu[4], in whose "Analyse Médicinale du Sang", published in 1776, is set forth the doctrine that not only every gland but every organ of the body elaborates a specific substance or secretion which passes into the blood stream, and that upon these secretions the physiologic integration of the body as a whole depends.

The literature on the thyroid, however, up to and through the eighteenth century has largely to do with the description of endemic goitre. Indeed it was through such enlargement that the thyroid became known in antiquity and we find many references to this change both in the classic and mediæval literature. Van Leersum[5] lately has pointed out that the Madonnas of the old Dutch, German, and Italian masters (fifteenth to sixteenth centuries) often show thyroid enlargement as do those of some of the artists of the nineteenth century. The term "bronchocele" is much used for goitre in the older literature, but Heister[6] pointed out that tracheocele would be more accurate. He also believed that cold water drinking was responsible, by chilling the parts during swallowing.

Of historic interest in the English literature are the papers of Prosser[7] who in 1769 described the "Derby neck", and Benjamin Moseley[8] who in 1800 described the "Alpine bronchocele". He believed the cause to be the frigid blast coming down into towns during the warm seasons, and the best preventive, therefore, was the guarding of the neck and throat. In the same year Benjamin S. Barton[9] wrote a memoir on goitre as it prevailed in North America, chiefly among the Oneida Indians of

New York. Barton believed the cause to be the miasmata of marshes.

Perhaps the most enlightened statement at this time is that of Fodéré[10] (1800) who described goitre as an indolent tumor of the thyroid which occurs principally in the inhabitants of the valleys at the foot of the secondary Alps. Each little grain of the gland, he says, contains a juice which is much increased in engorgement. Stagnation of this humor forms goitre. It may well be that this notion is not far from the truth. Fodéré also pointed out that in the past goitre was very frequently confused with scrofula.

Discovery of Exophthalmic Goitre

Of perhaps more interest to-day is the story of the development of knowledge of that peculiar syndrome now generally known as exophthalmic goitre in contrast to simple goitre. This syndrome, when fully expressed, is such a striking one that it seems hard to believe that it has not been known for centuries. Nevertheless, it is not until the beginning of the nineteenth century that we find any written accounts of it. In 1802 Giuseppe Flajani[11] of Rome, in his "Collezione d'Osservazioni e Riflessioni di Chirugia", relates the case of a young Spaniard who developed a tumor in the neck. This tumor, which he recognized as thyroid, extended laterally both to the right and left and had a median sulcus. It was accompanied by continuous dyspnœa and an extraordinary palpitation of the heart. The veins over this goitre were swollen as if varicose, and the patient was run down and emaciated. Here are at least two of the cardinal manifestations of the now well known syndrome, goitre combined with violent heart action. Flajani mentions having seen similar cases in all of which he obtained improvement by

the continued use of cold compresses. We should incline now to the belief that he had observed spontaneous remissions. Nevertheless, as he was a pioneer his observations are important.

A far more complete and clearer description, however, is that of Dr. Caleb Hillier Parry, the distinguished physician who practiced in Bath between 1780 and 1816. Parry's observations are recorded both in his "Elements of Pathology and Therapeutics"[12], published in 1815, and in his collected medical writings[13] published posthumously in 1825. The account in the latter begins with these words: "There is one malady which I have in five cases seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed, in that connection, by medical writers. The malady to which I allude is enlargement of the thyroid-gland."

Parry's first case (seen by him in 1786), which is the one of the series of which he gives the fullest account, showed the following symptoms and signs: palpitation, especially on exercise, increased force and frequency of the heart beat, full, hard and irregular pulse, rate 156, nocturnal attacks of dyspnœa and constriction in the chest with the spitting of a small quantity of blood, violent stitches of pain beneath the sternum, a large bilateral swelling of the thyroid, distention of the carotids, and exophthalmos. The description is sufficiently clear to establish with certainty the diagnosis of severe exophthalmic goitre, and indeed the only important manifestations, as we know the disease to-day, not specifically mentioned are tremor, sensation of warmth and increased appetite. Of the exophthalmos Parry says, "the eyes were protruded from their sockets, and the countenance exhibited an appearance of agitation and distress, especially on any muscular exertion, which I have rarely seen

equalled." Of the heart action he notes that "each systole of the heart shook the whole trunk of the body."

He cites four other cases with goitre, palpitation and violently beating carotids, and three others with goitre and palpitation. In none but the first is exophthalmos mentioned, and it is quite possible that several of them may have been the adenomatous type of goitre rather than the exophthalmic. Parry also reports a series of four cases which he terms "Bronchocele with Affections of the Head", in all of which goitre was associated with various nervous symptoms, headache, irritability, and in two with epilepsy as well.

Parry, as he states in his opening paragraph, was evidently chiefly impressed with a possible relation between violent heart action and goitre, and between goitre and cerebral manifestations. Of the thyroid's possible function he says, "that one can scarcely avoid suspecting that the thyroid gland, of which no use whatever has hitherto been hinted at by physiologists, is intended in part to serve as a diverticulum in order to avert from the brain a part of the blood, which, urged with too great force by various causes, might disorder or destroy the functions of that important organ" (the brain). In other words, although Parry's powers of observation are great, his deductions as to function are really less accurate than those Wharton made more than a century earlier.

The next account is that by Robert J. Graves of Dublin, published first in the "London Medical and Surgical Journal" in 1835[14], and second, three years later, in his "Clinical Lectures"[15]. He writes, "I have lately seen three cases of violent and long-continued palpitations in females, in each of which the same peculiarity presented itself — viz., enlargement of the thyroid gland; the size of this gland, at all times considerably

greater than natural, was subject to remarkable variations in every one of these patients. When the palpitations were violent, the gland used notably to swell and become distended, having all the appearance of being increased in size, in consequence of an interstitial and sudden effusion of fluid into its substance. The swelling immediately began to subside as the violence of the paroxysm of palpitation decreased, and during the intervals the size of the gland remained stationary. Its increase of size, and the variations to which it was liable, had attracted forcibly the attention both of the patients and of their friends. There was not the slightest evidence of anything like inflammation of the gland."

Graves goes on to say that the palpitation in all three of these patients had lasted more than a year and "with such violence as to be at times exceedingly distressing; and yet there seems no certain grounds for concluding that organic disease of the heart exists." In one patient he could hear the heart beating while at some distance from the bed.

"The sudden manner in which the thyroid . . . used to increase and again diminish in size, and the connexion of this with the state of the heart's action", led him to the interesting speculation as to whether the thyroid might not in fact be analogous to erectile tissue, and he made an interesting suggestion that in certain patients with so-called globus hystericus the phenomenon may not be purely nervous but rather the result of pressure from a sudden engorgement (erection as it were) of the thyroid. These enlargements of the gland are, he says, "essentially different from goiter in not attaining a size at all equal to that observed in the latter disease."

In his first three cases he makes no mention of eye signs, but in a fourth, a lady of twenty with enlarged thyroid, hys-

terical manifestations, tachycardia and asthenia, he observed that "the eyes assumed a singular appearance, for the eyeballs were apparently enlarged so that when she slept, or tried to shut her eyes, the lids were incapable of closing. When the eyes were open, the white sclerotic could be seen, to a breadth of several lines, all round the cornea."

In this case Graves notes also that there was a remarkable disproportion between the beats of the radial and of the carotid arteries, the pulsations of the former being comparatively feeble, while those of the latter were violent, causing a most evident throbbing of the neck and accompanied by a loud rustling sound.

Precisely the same observation was made independently by von Basedow [16], a district physician in the small town of Merseburg, Germany, who published in 1840 an excellent account of the syndrome. This writer reports four cases, all clearly exophthalmic goitre, and gives much more detailed descriptions than either of his predecessors. In his first case, for example, we find mentioned increased sweating, asthenia, emaciation, amenorrhœa, palpitation, tachycardia with small radial pulse, oppression in chest and dyspnœa, protrusion of eyeballs, exhilarated and careless mental attitude, together with enlargement of the thyroid.

His second patient showed asthenia, obstinate diarrhœa, loss of flesh, night sweats, marked protrusion of eyeballs, dyspnœa, oppression in breast, frequent small pulse, ringing heart beats, inability to keep hands quiet, hasty speech, sensation of intense warmth, excessive appetite, and a strumous swelling of the thyroid. The cardiac impulse became diffuse, and a saw-like noise was heard in the carotids. This patient finally improved, getting back a good state of nutrition and a fair degree of health, but the tachycardia and exophthalmos persisted.

Basedow's other cases were equally typical. In one of them

the extreme exophthalmos led to corneal infection and ultimately the loss of the sight of both eyes.

Exophthalmic goitre has been variously called after these four writers: Flajani, Parry, Graves, and Basedow. Flajani's account is so incomplete that to Parry really belongs the priority, and to Basedow the credit for the most complete description. Graves gives no hint of knowing of the work of Parry or Flajani, nor Basedow of that of Flajani, Parry or Graves.

Parry and Graves seemed impressed chiefly by the coincidence of an affection of the heart, mainly characterized by violent action, with an enlargement of the thyroid. Each cites a single case in which exophthalmos was also present. Graves made an advance over Parry in that he sensed clearly the extreme vascularity of the thyroid, as had Wharton, and in that he believed the heart affection to be purely functional. He further recognized that the thyroid enlargement in this syndrome was of a nature quite different from ordinary goitre. In his clinical descriptions, however, Graves adds but little to those of Parry; on the other hand Basedow gives intimate accounts of four cases of typical exophthalmic goitre, noting a number of manifestations which we regard as characteristic of the disease, but which do not appear in either Parry's or Graves' contributions. For example, we find mentioned for the first time increased sweating, asthenia, wasting, sensation of warmth, increased appetite, restlessness, mental excitement and irresponsibility, diarrhœa, in fact essentially all the classic symptoms and signs except the definite mention of tremor.

Basedow has much to say about the exophthalmos, the differential diagnosis from other types of exophthalmos and from other affections of the eye. He further states definitely that he regards this exophthalmos as a manifestation secondary to a

disordered circulation and dyscrasia or toxic state of the blood which exerts an action on the connective tissue back of the eyeball. He draws a parallel in this regard with the scrofula, which also stimulates connective tissue growth, and even hints that the syndrome may represent a special type of tubercle. Finally, Basedow states definitely that iodine is helpful in the treatment of these cases, though unfortunately he does not give his dosage. Parry had relied mainly on bleeding, and on squills and digitalis. It is interesting to note that directly following venesection he often found a marked reduction in the size of the thyroid.

The history of exophthalmic goitre may be divided conveniently into three periods. The first, which we have just described, extending from 1802 to 1840, comprising as it does the work of Flajani, Parry, Graves and Basedow, may be called the period of discovery. As we have seen it was largely one of description but with some attempts at interpretation, and its chief product may be said to be the so-called Merseburg triad, the clear recognition of the clinical relationship of three of the cardinal manifestations of exophthalmic goitre, namely goitre, exophthalmos, and rapid and violent heart action. The second period which we will now examine is one of further description and rather more interpretation (chiefly erroneous), and in it practically all of the symptoms and signs that we now know were recognized and described by such masters as Trousseau[17], Marie[18], and Charcot[19]. The third period is that of the development of the modern theories of the morbid physiology of the disease. This will be taken up somewhat later in our discussion.

The second period may be said to begin with the description in 1864 by von Gräfe[20] of the so-called lid lag. Von Gräfe stressed the fact that the lag of the lid behind the globe in downward rotation is independent of the exophthalmos. Either

sign may exist without the other. He believed it sympathetic in origin, due to an affection of the sympathetic innervation of the levator palpebræ.

In 1879 an attempt was made by Filehne[21] (so far as we can discover, the first) to produce the disease experimentally. This writer believing that the manifestations of exophthalmic goitre strongly suggest an abnormality of the sympathetic nervous system, partly paralysis, partly stimulation, concluded that the cause must lie in either the peripheral ganglia or the brain. Since there are marked vaso-motor changes and since the vagus centre is near the vaso-motor centre, he suspected the brain. To test his theory he either incised or cauterized the upper quarter of the inner portion of the corpora restiformia in rabbits. By these operations he claims to have produced some of the signs of Basedow's disease. Usually he got tachycardia and exophthalmos, occasionally goitre, never all three of these in one animal, but various combinations of two. The rabbits with exophthalmos also showed the sign of infrequent winking as is seen in human beings with Basedow's disease. The pupils were uninfluenced but ophthalmoscopic examinations showed dilated arteries in the fundi. He further found that if one enucleated the eye of a normal rabbit there was but little bleeding from the cut artery, but if one enucleated the exophthalmic eye, there was profuse bleeding. He believed, therefore, that the exophthalmos in his rabbits was due to engorgement behind the globe, and that the goitre likewise was due solely to engorgement. The tachycardia he considered due to reduction of vagus tone, and by analogy, he felt that human Basedow's disease was due to the same.

Of course we cannot accept this explanation in its entirety, but the observations are of interest, particularly those relating

to engorgement. Graves, it will be recalled, also sensed a marked increase in vascularity and engorgement of the gland in exophthalmic goitre. We know now that there is a true hyperplasia accounting for some of the increase in size, but still engorgement undoubtedly accounts for a certain portion of it.

The next important advance was the recognition by Pierre Marie[18] in 1883, confirmed by Charcot[19] in 1885, that tremor is a constant sign in exophthalmic goitre. This, added to the Merseburg triad, is often said to constitute the fourth cardinal manifestation of the disease. This tremor Marie describes as involving in the most marked cases the various muscles of the body but frequently it is found only in the extremities. Sometimes it is so marked as to interfere with the movements of the hands, sometimes so slight as to be only detectable by having the patient extend the fingers. It is rapid, about eight and one-half tremors per second, while those of paralysis agitans and senility are five to six. Marie also gives an excellent description of the disease and stresses a number of the now well known symptoms and signs: for example, the urinary manifestations — polyuria, glycosuria, albuminuria (of which glycosuria alone may be said to be characteristic) — also the diarrhœa which, as he points out, is of a peculiar sort being without colic, paroxysmal, and having a sudden beginning and ending. In addition increased sweating and a morbid and insatiable appetite are among the frequent symptoms, and angina pectoris, tachycardia, cough without expectoration, and such skin manifestations as pigmentation, vitiligo and urticaria also occur. Any of these taken singly Marie believes might be explained by a derangement of the sympathetic or vagus, but when one finds also cerebral symptoms such as epileptiform attacks, paralytic attacks, hemiplegia, paraplegias, hemian-

æsthesias and aphasias, as claimed by Ballet, and choreiform movements, hemichorea and nystagmus, as found by himself, it seems more reasonable to say that the disease is a *general neurosis* rather than a neurosis of any particular nerve.

Charcot is in general agreement with Marie, but has a somewhat different conception of the tremor, which he says differs from all those seen in neuropathology, being more rapid than senile trembling or that of paralysis agitans (eight to nine per second). The digits do not tremble by themselves; on the contrary the tremor is general. It puts in play all the great muscles of the trunk and members, but it does not appear that it ever occupies the muscles of the head or extremities. One observes in these parts only some movements of totality which are imparted to them by the rest of the body.

Charcot has much to say of Vigouroux' discovery that the electric resistance of the skin is decreased in exophthalmic goitre. He suggests that this might even serve as a quantitative measure of the intensity of the disease and as a means of differential diagnosis in formes frustes or atypical and borderline cases, much as we use the basal metabolism to-day.

We would end what we have called, for convenience, the second period in the history of exophthalmic goitre with the discovery and description of the last of the important eye signs by Moebius[22] (1886), the insufficiency of convergence known as his sign. It consists, so Moebius states, in an inability to converge on near objects of which the subject is unaware, for it produces no double vision but only a feeling of tension. It is not related definitely to exophthalmos and may occur in diseases other than exophthalmic goitre. He considered that there is no question of a true paralysis and that the exophthalmos alone cannot be the cause. He supposed that the exophthalmos made

the eye movement in general more difficult. The eye muscles, like other muscles, are asthenic in exophthalmic goitre and this weakness shows itself first in convergence, as might be expected, since this is recognized as the most strained eye movement.

Moebius[23] (1891) also discusses the other eye signs. The exophthalmos may be either an early or late sign and is not related definitely to the other phenomena. At death a pad of fat is found in the posterior part of the orbit. Stellwag's sign, which is the wide lid aperture and infrequent winking, signifies an increased tonus of the eye opening muscles. It may appear in maniacal states. Von Gräfe's lid lag appears on lowering, not on raising the eyes. Moebius suggests that it is a consequence of Stellwag's sign, for if the eye opening muscles are in increased tonus they will hold the lid back as the eyeball rotates downward, but will strengthen its return as the globe ascends. Von Gräfe's sign sometimes occurs in normal persons and sometimes is absent in exophthalmic goitre, so Moebius regards it as of but slight importance.

In order not to make too extended a chronological advance along a single path, we shall now leave the account of exophthalmic goitre for a time and instead trace certain other lines of thought on the problem of the thyroid and its ailments. It really was first through the recognition of the effects of thyroid underfunction rather than of overfunction, as in exophthalmic goitre, that the true function and physiology of the thyroid began to be understood, and the first form of underfunction that we find critically discussed is endemic cretinism.

Early Work on Hypothyroidism

The clinical picture of cretinism and its coincidence with endemic goitre, especially in Alpine countries, has been noted

by many writers. In 1848 Dr. Hugh Norris[24] reported a high incidence of undoubted cretinism in a goitrous village of Somersetshire. So goitrous indeed was this district that "the offspring of strangers acquire bronchocele, if they become residents in the place at an early age." All Norris' cretins possessed goitres as did most of the rest of the inhabitants of the village, and he gives his definite "opinion that the disease in question is not only accompanied, but in some measure caused, by the presence of goitre."

Two years later (1850) Curling[25] reported to the Royal Medical and Chirurgical Society of London two cases of sporadic cretinism, both of which came to autopsy. The first was a child of ten years, the second an infant of six months. Both showed the typical characteristics of cretinism including, which is especially remarked upon, swellings "at the outer sides of the neck, external to the sterno-cleido-mastoid muscles". At autopsy these swellings were found to be fatty, and in neither case *could any trace of the thyroid gland be found.*

By far the most illuminating contribution to the development of our knowledge of hypothyroidism is that of Dr. C. Hilton Fagge[26] from Guy's Hospital in 1871. Fagge reported four cases of sporadic cretinism; he gives excellent descriptions and calls attention to the similarity of this disease to endemic cretinism but for the striking exception the constant absence of goitre. Fagge believed his cases to be entirely similar to Curling's, and also noted the fat pads above the clavicles which he describes as soft, movable, inelastic swellings which appear to be connected with the subcutaneous rather than the deeper tissues. He believed that common idiots never present such swellings and that they are a constant feature in sporadic cretinism. One of Fagge's cases (No. 2) was apparently a

perfectly normal child up to eight years. Then, following an attack of measles, she gradually developed the appearance of hypothyroidism; her mental faculties, however, remained good.

The essential characteristics of sporadic cretinism are, according to these writers, somewhat as follows. The body is stunted, the head round, the face broad, the eyes are widely separated by the flat nose, the alæ nasi are thick, the nostrils rounded, the mouth large and generally open, and the lips are thick. The hands and feet as well as the fingers and toes are short and broad. When sporadic cretinism is congenital (in contrast to Case 2 cited above where it was apparently acquired), there is as in endemic cretinism deficiency in mental power. In the endemic form there is goitre; in the sporadic, wasting or absence of the thyroid body. Sporadic cretinism may be in the offspring of healthy parents. There is no relation to rickets, scrofula or inherited syphilis.

Fagge's discussion of his subject is distinctly penetrating. Observing that most cases of sporadic, like endemic cretinism, are congenital, he yet clearly recognized in the experience of his Case 2 that the condition might be acquired, and he goes on "to speculate as to what characters would be present, should the disease (if that be possible) arise still later in the course of adult life. The peculiarities in the form of the cranial and facial bones, and in the bony framework generally, would then probably be absent, the development of the skeleton being unalterable when once completed." He concludes that the most marked features in such a case "would be a coarseness and thickness of the soft parts of the face (especially the lips), and perhaps of the subcutaneous tissues of the hands and feet, besides the presence of the supra-clavicular fatty tumours, and possibly a wasting of the thyroid body, if that should prove to

be a constant character of the disease." In other words, we have a good description of adult myxœdema by a man who had never seen a case!

That the symptoms and signs of sporadic cretinism were due to the absence or wasting of the thyroid he firmly believed, and for the apparent paradox that in endemic cretinism the same signs and symptoms are present with goitre, he offered a very keen explanation. "Goitre", he says, "prevails endemically in many parts of England where endemic cretinism is unknown. Goitre is the earlier effect of the endemic influence; cretinism shows itself when the action of that influence is intensified by operating on more than one generation. From these facts it would be expected that the individuals most severely affected with cretinism would invariably have very large goitres; but observation shows that the exact contrary is the case. In the worst cretins the thyroid body is often no larger than natural; while persons with enormous tumours are frequently well developed, both physically and mentally, although they and their ancestors have long resided in the same neighborhood, exposed to the morbific agency." He further suggests, "that when a large goitre exists, it may possibly have the power of protecting against the more severe effects of the endemic influence; and thus that cretinism is associated with an enormous bronchocele only when the exciting cause is present in a very intense degree." In the case of sporadic cretinism with absence of the thyroid "we have but to suppose that the healthy thyroid body is capable of exerting such a counteracting influence, and that in most parts of England the cause of cretinism acts only with a low degree of power; and we can then at once see why a form of cretinism should show itself when the thyroid body is atrophied."

The first actual report of adult myxœdema seems to be that of Sir William Gull[27], also of Guy's, whose paper "On a Cretinoid State supervening in Adult Life in Women" was published in 1874. Gull describes two cases of a morbid state of which he had seen five and of which he is "not able to give any explanation of the cause. . . . It is unassociated with any visceral disease, and having begun appears to continue uninfluenced by remedies." Its characteristics are "languidity", increase in bulk, roundness of face, very smooth skin of fine texture, and a delicate rose purple color to the cheeks. The cellular tissue under the eyes is loose and folded, that under the jaws thick and folded, the lips are large, the alæ nasi thick. The eyes appear wide apart. The nose is so deformed as to make the face look flat. The hair is soft and flaxen, the expression remarkably placid. The tongue is broad and thick, the voice guttural, the pronunciation is as though the tongue were too big for the mouth; the hands are broad, thick and spade-like. The integuments of the chest and abdomen are loaded with subcutaneous fat. The upper and lower extremities are also large and fat with traces of œdema which pits doubtfully on pressure. The description indeed is essentially complete except that no mention is made of chilliness or absence of sweating.

This syndrome of adult cretinism or myxœdema (mucous œdema), as it was named six years later by Dr. W. M. Ord[28], has often been referred to as Gull's disease. Gull indeed was first to report actual clinical cases, but hazarded no guess as to the cause of the ailment. How much greater was the accomplishment of Fagge who, on the other hand, recognizing a certain pathogenesis in infants, was able to imagine its results in adults and so to describe excellently a syndrome not yet observed.

Autopsies on untreated cases of myxœdema are not abundant in the past, and since the discovery of the remedy they have been exceedingly rare. One of Ord's cases came to autopsy and is probably the first in the literature. The findings were as follows. The kidneys were of normal size, rather tough in consistence, and not notably discolored. The cortical portion was a little wasted, but the capsule was not adherent. The arteries were everywhere greatly thickened, there was much atheroma in the larger vessels, and the heart was much hypertrophied on the left side, weighing sixteen and a half ounces (513 grams). There were no other important naked-eye appearances excepting in the thyroid gland, which was reduced to a third of the natural size, and was tough and fibrous looking on section. Under the microscope a remarkable overgrowth of the fibrillar element of connective tissue was found in all parts of the body, the fibrils being separated from one another by much larger intervals than usual, and the interspace being filled by a transparent material yielding mucin, an excess of the normal cement, with excess of nuclei.

The function of the thyroid has aroused men's curiosity for centuries. Sir Victor Horsley[29], for instance, has collected some ten theories as to function, beginning with those of Wharton which have already been cited.

Perhaps the most enlightened paper on thyroid function considering the date of writing, 1836, is that of T. W. King[30] of Guy's Hospital. This investigator noted the lobular arrangement of the glands and the acini (cells, he called them) and also a gummy, translucent fluid, coagulable by alcohol or boiling contained in the latter. He observed that this fluid possessed a much higher albumin content than blood serum. He was much impressed with the enormous blood supply to and the

extreme vascularity of the thyroid, and was very close to suspecting its true function as can be inferred from the following remarks. "Like all parts, it requires to be nourished; but, unlike some parts of the same class, its nourishment does not seem to be the main intention of its vascular supply." Again, "Whilst the nourishment of a part is indispensable to its existence; the influence which it exerts upon the circulating fluids may be more or less needful for the healthful subsistence of the entire animal." And a little further on he surmises that, "We may one day be able to shew, that a particular material principle is slowly formed, and partially kept in reserve; and that this principle is also supplementary, when poured into the descending cava, to important subsequent functions in the course of the circulation."

It requires only slight paraphrasing of these statements to arrive at the modern conception that the gland secretes an autacoid, thyroxin, necessary to normal existence, which is stored in the colloid of the acini and later enters into the circulation for distribution to all parts of the body.

The determination of the function of an organ by observing the effects of its extirpation has always been a crucial method. The first extirpations of the thyroid seem to be those of Sir Astley Cooper[31], 1836, in puppies. It does not appear certain, however, from Sir Astley's account that he was intent on the symptoms which might follow operation. He had been interested in a fluid which he had, as had King independently, obtained from the thyroid, and his remarks centre chiefly about that. Cooper's puppies survived thyroidectomy but developed no manifestations which we should consider suggestive of hypothyroidism.

It was left for J. M. Schiff[32] of Geneva in 1859 to demon-

strate for the first time undoubted hypothyroid symptoms in animals following extirpation of the thyroid. This work was confirmed by Zesas[33] in 1884.

It was also in goitrous Switzerland that human thyroid surgery was largely developed, and there too, in consequence, that postoperative hypothyroid symptoms were first noticed. There has been considerable controversy respecting the claims of the two surgeons, J. L. Reverdin of Geneva and Theodor Kocher of Berne, for the actual discovery of such a syndrome. It is probable, as is usual in such controversies, that each deserves some credit. Reverdin[34] in September, 1882, in a very brief note states that he had seen such symptoms as weakness, anæmia and œdema of hands and face without albuminuria, coming on in two to three months after complete thyroidectomy for goitre. In April, 1883, Kocher[35] in a far more complete report described symptoms closely resembling Gull's disease, which in his experience had usually come on in patients upon whom he had done complete thyroidectomies. Lassitude, weakness and heaviness of the limbs were complained of shortly after the patients left the hospital, and soon after coldness and swelling of the extremities, and slowness of thought and speech. "The whole face is thickened, there is a transparent swelling of the lids, such as is seen in certain cases of nephritis, the nose becomes thick, the lips are enlarged and coarse. Also the hands and feet appear coarser and thicker; in rare cases there is œdema of the calves and ankles.

"The trunk, too, becomes amplified; this is especially noticeable in girls in the neighborhood of the waist. The lower part of the thorax appears widened, the abdomen large. Only in the rarest of cases is this largeness due to demonstrable ascites. We could ascertain the presence of the latter in two

cases only, in which there was at the same time obvious œdema of the legs.

"The skin shows a change connected with the tumefaction of certain parts of the body. As in cases in which œdematous swellings have existed it becomes slightly infiltrated, its suppleness is lost, it can only be raised in thicker folds. Its surface is dry; there is often very conspicuous peeling from the cheeks and ears. In connection with these epidermic changes there is falling off of the hair on the head, which was, especially in two cases, very much marked; the hair only scantily surrounds the top of the head, it is thinner and less supple than under normal circumstances. The baldness considerably contributes towards the cretinoid appearance of the affected individuals, inasmuch as the body seems to belong to a child, the head to an old man.

"Very great anæmia is observed in the more advanced cases. The skin and mucous membrane, especially of ears and lips, are pale; the pulse remarkably small, sometimes thready, easily compressible." *

Kocher remarks upon an obvious close relationship between the syndrome and idiocy and cretinism; for it he suggests the name cachexia strumipriva. Directly after the appearance of Kocher's paper, Felix Semon[36] of London (November, 1883) pointed out the likelihood "of a common condition, probably a causative factor, in Myxœdema, cachexia strumipriva and cretinism, viz. loss of the function of the thyroid body".

In 1884[37] Schiff returned to the problem of thyroidectomy. Using antiseptic methods, which had not been known at the time of his first work, he found that in rats thyroidectomy could

* This translation was taken from Clinical Society's Transactions, Report on Myxoedema, Suppl. to Vol. XXI, page 91 (No. 40 in Bibliography at end of this chapter.)

be done without a single death and with relatively little effect. In cats and dogs, on the other hand, it was rapidly fatal, and we may infer from the symptoms he describes that tetany due to simultaneous parathyroidectomy played an important part. He concluded, however, that the importance of the thyroid varied among different species of mammals. More important than this was his discovery that thyroidectomy loses its dangers and the essential part of its effects if one first introduces into the abdominal cavity the thyroid from another animal of the same species. This work seems to be the first successful use of substitution therapy.

In 1885, following close on Schiff, a more perfect imitation of human myxœdema or cachexia strumipriva was obtained by Sir Victor Horsley[38] by complete thyroidectomy in monkeys. These, after about five days of anorexia and fibrillary twitchings, became languid, paretic and imbecilic. They developed puffiness of the eyelids and belly, subnormal temperature and pallor. Altogether the resemblance to human myxœdema was sufficiently close to warrant the conclusion that the disease is due to thyroid lack.

The discoveries of Kocher, together with some confirmatory work by Paul Bruns[39] in England, had led in December, 1883, to the appointment by the Clinical Society of London of a committee to consider and investigate the whole subject of myxœdema. This committee, which included such men as Ord, Halliburton, Horsley, Semon, and others, produced in 1888 a monograph[40] containing a vast amount of data bearing on the clinical, the pathologic, and biochemical phases of the disease based on a detailed analysis of one hundred and nine clinical cases and the experimental work of Horsley. The symptoms were described essentially as we know them to-day

and need not be discussed now, but the pathologic findings may be mentioned, for since treatment has been discovered practically no autopsies on untreated myxœdematous patients have been reported. The series shows the only common lesion to be atrophy of the thyroid. This begins as a small cell infiltration in the walls of the vesicles and this is followed by epithelial proliferation in the vesicles themselves. In the more advanced stage the gland becomes converted into a delicate fibrous tissue in which small islets of round cells are sparsely placed. The skin often showed nuclear hyperplasia and development of connective tissue. The patient's increased bulk is due to increase in subcutaneous fat. The pathologist's conclusions were that myxœdema is dependent on a destructive lesion of the thyroid, and that the changes in the skin are frequent and probably in the later stages constant. These changes were considered not passive but as indications of irritation, or resembling inflammation. The general conclusions reached by the committee, most of which have stood the test of time, were very briefly to the effect that myxœdema is a well defined disease probably identical with sporadic cretinism and cachexia strumipriva, closely related to endemic cretinism and due to a loss of function of the thyroid gland, the ultimate cause of destruction or loss of function not being evident.

Along the thyroidectomy line of study the final step was taken when Gley[41] in 1891 showed that the nervous phenomena found by various experimenters — chronic convulsions, muscular agitation, paralyses, etc. — only occur if certain glandules found on either side of and behind the thyroid, which he quotes Sandström as having discovered and named parathyroid in 1880, are removed as well. Thus was tetany, due to parathyroid lack, finally separated from myxœdema, due to thyroid lack, and the

knowledge of the physiology of these glands accordingly clarified and advanced.

Discovery of Substitution Therapy

In the next few years rapid strides were made chiefly by clinicians in the field of opo- or substitution therapy. In 1890 Bettencourt and Serrano[42] report the relief of symptoms by the graft of half a sheep's thyroid under each breast. In 1891 Vassale[43] reported the prevention of cachexia strumipriva in dogs after complete thyroidectomy by the intravenous injection of an extract of their own thyroids. In the same year Murray[44] reported a case of subcutaneous injection of an extract of sheep's thyroid, and recommended the method for the general treatment of the disease. In the same issue of the "British Medical Journal" Fenwick[45] also reported a patient with myxœdema to whom he had given thyroid juice subcutaneously. The result, which seems to have impressed him most, was the marked diuresis which at once occurred, and he did not, as did Murray, recommend the treatment to the profession as a treatment for myxœdema.

The next step, the discovery that the oral administration of thyroid constitutes a satisfactory substitution therapy, was also made simultaneously by two independent observers, their papers likewise appearing in the same number of the "British Medical Journal" in 1892. These were Mackenzie[46] and Fox[47]. Both got satisfactory results by feeding thyroid to myxœdema patients, and both got what we should regard as hyperthyroid symptoms when the amount fed was too large. Fox cooked his thyroid which seemed not to interfere with its activity. So much for the discovery of substitution therapy in the Western World. We should note, however, that Hume[48] has recently

stated that the Chinese employed the feeding of sheep's thyroids for cretinism as early as the sixth century A.D., and that the practice is familiar to all housewives throughout China.

Nature of the Thyroid Secretion

In the last chapter on the nature of the active principle of the thyroid we have the discovery by Baumann[49] (1896) that iodine is a normal constituent of the gland, and that the iodine content and concentration rapidly increase if iodine is ingested. It had been known long before this that the administration of iodine salts often caused a diminution in the size of goitres. Coindet[50], for example, in 1820, noting that both the marine alga, Fucus vesiculosus, and dried sponge had been successfully used in the treatment of goitre, concluded that the only principle common to these two was iodine, and so tried iodine salts and found that they worked.

Regarding the iodine relationship the next important step after Baumann was Marine's[51] (1907) demonstration that iodine is necessary for normal thyroid function and that endemic goitre is to all intents and purposes to be regarded as a deficiency disease, deficiency of iodine. Finally in 1915 came Kendall's[52] great discovery, the isolation from the thyroid in crystalline form of a compound containing 60 per cent. iodine and having apparently the full physiologic activity of whole thyroid gland. In 1917, for this new hormone, called thyroxin, a structural formula was proposed[53]. Thus at last the true function of the gland emerged, namely the production and delivery to the blood of this iodine bearing autacoid, and so far as our knowledge goes at present this may be said to be the only function, for no evidence has yet been obtained that the organism with thyroid intact is capable of any activity different

from the thyroidless one supplied with a sufficient quantity of thyroxin. The modern view of the normal and morbid physiology of the thyroid, therefore, may be said to centre about the action of thyroxin on the organism and the factors which control its manufacture.

Further Work on Toxic Goitre

We now have left for consideration the third period in the development of knowledge of exophthalmic goitre. We closed the second period with the discovery by Moebius of another eye sign. We may open the third with his development of the thyrotoxic theory of the disease (1891)[23]. The French writers, it will be recalled, had regarded it as primarily an affection of the nervous system or neurogenous in origin. Moebius believed that while persons with neuropathic natures were more likely to develop the disease, to say that it belonged to the family of neuropathies was going too far.

He calls to mind that, whereas thyroidectomy causes a syndrome identical with spontaneous myxœdema, Basedow's disease, on the other hand, is in many respects the antithesis of myxœdema; hence the idea that it is related to an excessive function of the gland. He notes certain similarities and certain striking dissimilarities in the two diseases. Both are chronic and afebrile, both usually fatal (fortunately now neither should be), both attack chiefly women in middle life (not true of the recent experience with exophthalmic goitre in the United States). In both there is alteration in thyroid and cardiac activity, in the mentality and in the skin. In the one the thyroid is enlarged, in the other atrophied; in the one the heart is rapid, in the other slow; in the one the skin is thin, warm and moist, in the other cold and dry; in the one there is cerebral

excitability, in the other stupidity and retardation. If myxœdema, therefore, is due to a disturbance of the thyroid, is not this the case with Basedow's disease as well? A further point in favor of such a view, he notes, is that operative removal of a portion of the goitre in Basedow's disease often is beneficial. He concludes with the wise observation that of the cause of the primary thyroid disturbance nothing is known, and indeed in this respect we are now no better off than he.

We may next turn to the work of Friedrich Müller[54] (1893) whose studies of exophthalmic goitre really opened the way to an understanding of the rôle of the thyroid or its hormone in the regulation of metabolism in several of its phases. In connection with a detailed clinical and post mortem examination of five cases, he describes and discusses nearly every phase of the disease, but perhaps of most significance are his demonstrations of thyroid hyperplasia as manifested by high columnar epithelium and diminished lumina of the acini, and his discovery in one of his cases of an increased rate of protein metabolism. He also infers from the paradox of an increased ingestion of food combined with loss of weight, that there must be a metabolic anomaly, an accelerated katabolism in Basedow's disease.

That the thyroid was at fault Müller clearly believed, and that it is not merely engorged with blood, as Filehne had suggested, is proved by the histologic evidences of hyperplasia; yet he thought there was another factor. The nervous phenomena are so impressive that it is difficult to interpret them as due to other than organic central nervous system disease. But the evidence for a focal nervous lesion, he regarded as far from convincing, and considered that the causative agent was much more likely of a toxic nature affecting the nervous system

widely, as might the known poisons, alcohol, lead, or iodine. Thus he was led to conclude that for the production of exophthalmic goitre two factors are necessary, a neurogenous and a thyrogenous, or in other words, an hereditary or acquired neuropathic disposition plus a sickness of the thyroid. This view remains tenable to-day, although we should modify the theory he advances that the metabolic acceleration is dependent upon the nervous changes.

Müller's view very shortly was confirmed abundantly by Magnus-Levy[55] who showed beyond doubt that total katabolism, as measured by the gas exchange, is increased over normal not only in exophthalmic goitre, but also in normal persons on the ingestion of thyroid gland. A little later he showed that the converse is true in myxœdema. Thus is Moebius' conception of an antithetical relation between Basedow's disease and myxœdema, based upon his impressions of the symptomatology, splendidly justified by the demonstration of a fundamental physiologic variation dramatically opposite in the two. The importance of Magnus-Levy's discoveries can hardly be exaggerated; they, together with Müller's introduction, so to speak, mark the beginning of our present concept of thyroid function, and make possible the interpretation of a greater portion of the clinical symptoms and signs of these diseases in terms of their known morbid physiology.

In addition very recently Aub and collaborators[56], at the Massachusetts General Hospital, have demonstrated an increased rate of calcium and phosphorus metabolism in thyrotoxicosis, and a decrease in myxœdema: in other words, still another metabolic antithesis between these ailments. Thyroid administration in normal persons likewise caused an acceleration in the output of these elements. Step by step, therefore, have come

the discoveries of 1) increase first of nitrogen, then respiratory and finally inorganic salt metabolism when the thyroid overworks or when thyroid gland is fed, and 2) decrease of these same in hypothyroidism. These studies really form the foundation of our knowledge of the physiologic action of the thyroid hormone, namely, as Plummer[57] has claimed, that of a catalytic agent accelerating oxidative processes in all tissue cells.

In 1914 Cannon and his coworkers succeeded in producing in cats a syndrome very like exophthalmic goitre by fusing the phrenic nerve with the cervical sympathetic. In the light of present knowledge, it seems likely that in Cannon's experiment the hook-up was through the pituitary. Certainly a syndrome closely resembling exophthalmic goitre can now be produced by means of anterior lobe extracts.

In 1923 Plummer[62] showed that iodine exerts a characteristic influence upon the intensity of thyrotoxicosis manifested by fall in metabolic rate and improvement in symptoms. This has profoundly influenced the management of toxic goitre.

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CHAPTER II

FUNCTIONS AND DISEASES OF THE THYROID

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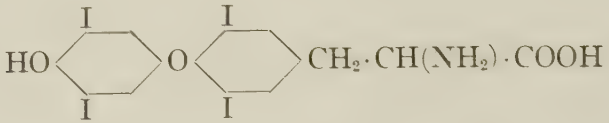
Function of the Thyroid

The correctness of one's impression of the nature of a derangement of any organ depends upon the accuracy of one's knowledge of the normal function of that organ. The thyroid gland is evidently not essential for life, since many species are without it, and others may still live after its removal. As Marine[1] has well said, "Broadly defined, our present conception of the function of the thyroid is that it provides the means, through its iodine containing hormone, of maintaining a higher level of metabolism than would otherwise obtain and also through fluctuations in its activity it provides a means for varying the rate of metabolism to meet changing physiological needs". In other words, so far as we know, the only function of the thyroid is the manufacture of thyroxin; and the action of thyroxin is probably, as Plummer[2] has claimed, that of a catalytic agent accelerating metabolism in all cells of the body.

This hormone, discovered and isolated in pure form by Kendall in 1915[3], has recently been synthesized by the English investigators Harrington and Barger[4], and its structural formula found to be



Morphologic Considerations

The grosser architecture of the thyroxin factory is well known; its peritracheal position and shield, or better, butterfly shape, also its origin from the floor of the embryonic pharynx[5]. In the next chapter these matters will be discussed briefly in relation to the general principles of examination and surgical treatment. Of interest now in relation to thyroid function are the facts that the gland has a very rich blood supply, and that its nerve supply is derived from the cervical sympathetic cord and from the superior and recurrent laryngeal nerves[6]. Of its circulation it can be said that the whole volume of blood of the normal human being (in the neighborhood of five liters) passes through the thyroid once an hour; it passes through the kidneys once in five minutes, and through the lungs once a minute.

The secretory unit of the gland is the follicle, a roughly spheroidal closed sac with a wall of low columnar or cuboidal epithelium. The follicles are derived from solid masses of the embryonic endodermal cells, which later acquire a lumen and become filled with the characteristic hyaline material, the so-called colloid, secreted by the cells. G. E. Wilson[7], working in Bremer's laboratory, recently has made wax reconstructions of the lumina of follicles in several thyroids, normal and patho-

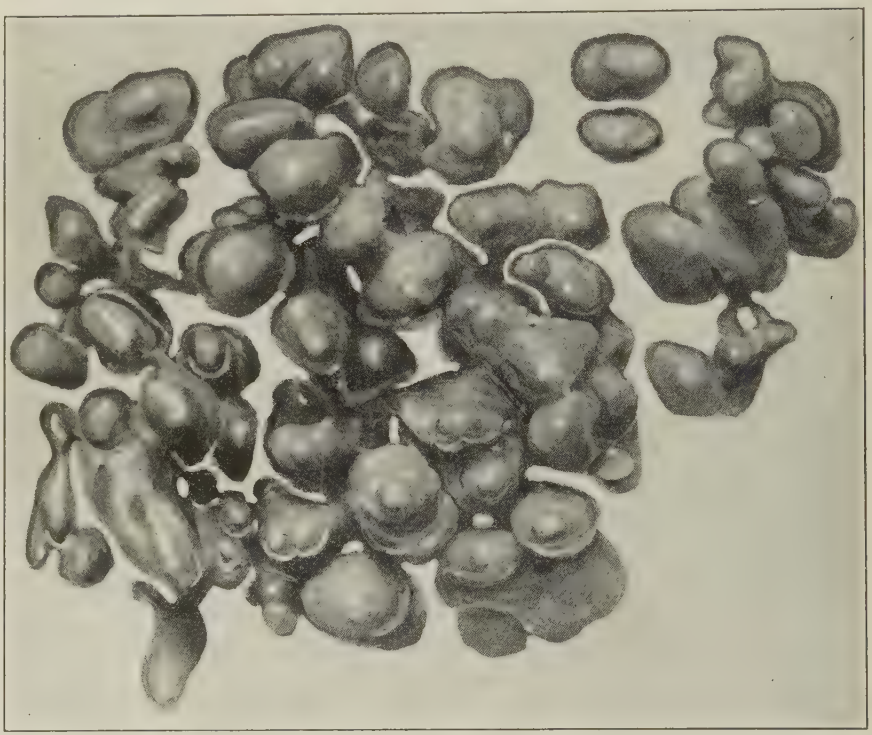


FIGURE 1. *Normal Human Thyroid.* Wax reconstruction of the follicular lumina by G. E. Wilson, who remarks, "The normal thyroid follicle has been found to be a more or less discrete, round, oval, or budded structure, averaging 300μ in diameter, and the variation in size is less than in all types of diseased thyroid gland."

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logic, which give an excellent idea of the spatial relations of these structures. We are indebted to him for photographs of several of these; that of a normal gland is shown in Fig. 1. It will be seen that there is considerable variation in shape and size, but less than in the pathologic glands figured in later chapters.

The parenchymal cells of the thyroid are similar to those of other glands, having large spherical or oval, reticular nuclei, and cytoplasm in which by special staining methods the so-called mitochondria and Golgi apparatus can be demonstrated. These structures appear to have some definite relation to secretory activity. In toxic goitre the mitochondria are increased in number[8], and the Golgi apparatus is hypertrophied[52]. In the dogfish the epithelial cells of the thyroid, so Cowdry[10] has shown, are flagellated. In the human being the epithelial cells are in direct contact with vascular endothelium without the intervention of a basement membrane. There are also certain interfollicular cells, which Williamson and Pearse[11] have described as large and at times stellate, and which they believe to be of endothelial origin and similar to the Kupffer cells of the liver. Their function remains quite unknown.

The activity of the thyroid, as judged from its histology, seems to undergo certain definite changes, in man at different age periods, and in some species at different seasons. Diet has an important influence on the thyroid structure and function, and some diets are actually goitrigenic. For further discussion of this see Chapter IV.

Thyroxin Secretion and Requirements

The amount of thyroxin which must be produced daily has been calculated by Plummer and Boothby[13] from the

amount found necessary, when injected intravenously, to maintain the metabolism of completely myxœdematous patients at a normal level. They conclude that it lies between 0.2 and 0.4 mgm., also that the total amount of active thyroxin in the body is from 12 to 14 mgm.

In other words, if an individual were completely thyroidectomized, and if enough time were allowed to elapse for him to reach a thyroxinless state, it would then require an initial injection of about 14 mgm. and a daily ration of less than 1 mgm. to keep him on a normal metabolic plane. Boothby and Sandiford[14] have estimated the catalytic power of thyroxin, in terms of energy, to be about 1000 extra calories for every milligram of the hormone. This, we may add, will not of necessity be the result in the individual still possessing some thyroid function, because the injected thyroxin may be stored by the normal gland. In this connection Uhlenhuth[15], for example, thinks that, "It is possible that the organism when in possession of a normal thyroid gland is able to regulate in some way the amount of hormone circulating in the blood, even if there be introduced an excess of it from outside".

Thyroxin is undoubtedly elaborated in the parenchymal cells of the thyroid, and probably reaches the blood stream through both lymphatics and veins. Studies of the thyroglobulin content of blood and lymph from the thyroid have been made by Carlson, Hektoen and Schulhof[16], and by Hicks[17], by means of thyroglobulin antiserum. Hicks found about the same concentration in the blood as in the lymph coming from the gland, but concluded that the blood stream was the more important pathway since the volume of flow there was much greater.

Of the concentration of thyroxin in the circulating blood

very little is known. Hunt[54] has obtained a little evidence by means of an indirect method, namely, the increased resistance to the toxic effects of acetonitril conferred upon mice by thyroid, that the concentration of the hormone may be increased in the blood of patients with Graves' disease. As he finds that agents other than the thyroid hormone affect the reaction, his evidence is difficult to interpret.

Veil and Sturm[55], however, have studied the blood iodine in man and found that it undergoes changes not only in disease, but in health at different seasons. During the summer months normal subjects showed an average of 0.0128 mgm. of iodine per 100 c.c. of blood, and in the winter 0.0083 mgm. Of this two-thirds was organically bound. In simple goitre low figures were obtained, in exophthalmic goitre high ones. Exogenous factors played but a small rôle in determining blood concentration. In exophthalmic goitre the iodine in the blood is high, of which the major portion is insoluble in alcohol. In addition Curtis[56] has shown that there is a high urinary excretion of iodine in this disease.

The parenchymal cells of the thyroid secrete colloid also. That process can be observed beneath the microscope, but what purpose the colloid may serve is far from perfectly understood.

The direction of secretion is usually towards the lumen. Colloid can be observed in actual transit from cell to follicular space. On the other hand, colloid is seen occasionally in the surrounding tissue spaces or vessels. Since the quantity of colloid stored in the follicles clearly can be influenced by iodine or lack of iodine, and since iodine is an essential constituent of thyroxin, it seems fair to conclude that colloid formation and storage is in some way related or subservient to thyroxin func-

tion. It may serve as a reservoir either for thyroxin or for iodine compounds to be used in its synthesis.

It has also been shown by Abel and his associates[21] that tryptophan, as well as iodine, is as necessary for the normal function of the thyroid as it is for that of the body as a whole; and that the thyroid has an avidity for this substance as it has for iodine, thereby enabling it to take sufficient quantities from the blood to meet its needs even when the total amount is so small that other tissues suffer from its lack.

The amount of thyroxin elaborated per day, as has been said, can be reckoned from observations upon metabolism, but of the rate of colloid storage and withdrawal from storage nothing thus far has been learned. About all we can say is that under normal conditions there must be a balance between colloid formation and its removal or destruction, for the total amount and the size of the gland remain essentially constant. Nevertheless, under certain circumstances there may be rapid fluctuation in amount of colloid stored, so that we must conclude that colloid balance, though usually stable, is potentially labile.

The reversible polarity of the cells suggests a mechanism whereby a very wide range of function becomes possible, secretion being directed towards the general circulation or towards the store house, as bodily needs may at any moment determine.

Various attempts have been made to discover the mechanism controlling the rate of thyroxin secretion: Is it chemical, nervous, or both? So far the results have been inconclusive. Engel[22] believes that the sympathetic causes vasodilatation in the thyroid, and that it is to be regarded as its secretory nerve; and Cannon[23] has shown that stimulation of the sympathetic cord produces an action current within the gland indicative of secretory activity. Hicks[17], on the other hand, could produce

no change in the thyroglobulin output after electrical stimulation of the sympathetic nerve, whereas iodine administration does produce an increase. Crawford and Hartley[24] find that sectioning of the vagus or sympathetic produces no alteration in the phenomenon of compensatory hypertrophy following partial thyroidectomy, and that stimulation of the vagus or sympathetic causes no histologic changes in the gland[6].

Action of Thyroxin

The outstanding effects of thyroxin are upon metabolism and growth and are conditioned doubtless, as Abel[25] has claimed for hormones in general, by the functional or chemical state of the organs acted upon. Those on metabolism are fundamental and universal, that is to say, exerted throughout all living tissues. Boothby[26] has put it, "that thyroxin can be considered as a calorigenic agent which increases the metabolic rate in proportion to the quantity actively present (the concentration) in the cells of the body". This, however, is hypothetical. The intact warm-blooded animal possessing a thyroid burns food substances at a very constant basic rate, the so-called basal metabolism, which will become higher if thyroxin or thyroid substance is fed, and lower if the gland is removed. Oxidation, however, as has been pointed out, does not cease in the thyroidless animal; it merely sinks to a minimal level. Whether this means that oxidation can take place in the absence of thyroxin, or whether tissues other than the thyroid can elaborate this hormone, is unknown.

The increased catabolism following thyroxin administration, which we can demonstrate by increased intake of oxygen and output of carbon dioxide, probably is chiefly, if not entirely, due to increased combustion of carbohydrate and fat, for

Boothby and associates[27] have shown that thyroxin feeding will not elevate permanently the output of nitrogen. From this Kendall[28] concludes that thyroxin affects metabolism chiefly through its action on hydrogen. But thyroxin, as Aub and his associates[29] have shown, accelerates the exchange of the inorganic ions of calcium and phosphorus. These investigators found, for example, that on a constant and low calcium intake of about 0.35 gm. the negative calcium balance of normal persons increased from about 0.45 gm. to about 0.80 gm. after large doses of thyroid. Patients with exophthalmic goitre when on this diet had larger negative balances (average 1.86 gm.) than normal persons (average 0.43 gm.), while those with myxœdema had smaller ones (average 0.25 gm.).

The effect of thyroxin on the general metabolism persists for a considerable time. Thus thyroxin administered to a myxœdematous subject causes an elevation in metabolism which persists from 70 to 80 days, and following cessation of thyroid administration in a myxœdematous subject, a similar period of time is required for the metabolism to make its maximum drop. The same is true following total thyroidectomy. However, the effect of thyroxin in a normal person is much shorter, lasting two weeks or less. We must look upon the thyroid as a regulator of metabolism over considerable periods of time, and consequently as a mechanism not adapted to furnish a sudden increase in metabolism for emergencies. This action should be contrasted with that of epinephrin, which may produce a sudden increase of metabolism of short duration[30].

Thyroxin also has an important influence over the distribution of body water, tissue colloids and electrolytes. Thompson[31], for example, has found in myxœdema patients on and off thyroid a certain parallelism between total plasma

volume and basal respiratory metabolism. As the basal oxygen intake rises under the influence of thyroxin or thyroid, the quantity of water in the blood stream rises too, and when thyroxin or thyroid is omitted, they both fall. Coincident with these phenomena Thompson finds a drop in plasma protein, and in most cases an increase in plasma chloride as the total plasma volume rises, and vice versa. Several myxœdema patients also have shown a fall in plasma bicarbonate along with the increase in volume. Similar changes in protein and chloride seem to be reflected in the spinal fluid. Thyroxin also influences creatine metabolism, there being a creatinuria in toxic goitre and an increased creatine tolerance in myxœdema.

A fundamental action is also exerted by thyroxin upon the nervous system. Cerebral activity in its absence falls to a low level, and the irritability of the nervous system is much reduced. This is seen typically in the disease myxœdema.

The effect of the hormone upon peristalsis is striking, and probably exerted through the nervous system. It can be studied well by means of information regarding the bowel movements of patients. For example, persons with myxœdema (hypothyroidism) are characteristically constipated, but as a rule this constipation disappears when thyroid is administered. We have also seen a considerable number of persons not myxœdematous, but having permanent low rates of metabolism, who are habitually constipated, and in whom regular bowel action promptly followed the taking of small doses of thyroid. In certain patients with exophthalmic goitre, moreover, we have obtained the story of habitual constipation until the illness commenced, after which the bowels were regular. Finally, in a large number of exophthalmic goitre patients there is the story of actual diarrhœa developing along with other symptoms.

In the adult mammal, then, an adequate supply of thyroxin is necessary for normal energy exchange, salt metabolism, and water, electrolyte and colloid distribution, and for a normal action of the nervous system and the organs under its control; in the growing individual it is necessary for growth as well. The adult, deprived for a time of thyroxin, although suffering extensive changes in consequence, becomes its former self again in all respects when the supply of the hormone is restored. But during the period of growth thyroxin shortage may give rise to retardation of development, especially in the bony skeleton and brain, which never can be offset entirely by subsequent adequate supply, or even excess of the hormone.

It is, however, in certain lower forms, the metamorphosing amphibia for instance, that the developmental rôle of thyroxin is most characteristically seen. So remarkable is its action in these species that Uhlenhuth[15] has been led to ask, "Does the thyroxin actually, as Kendall claims, merely increase the reactions going on also without it in the organism, without changing or adding any reactions, and must we think that a mere quantitative change is able to produce all that multitude of new forms and structures that we see arise in a thyroidless organism after the administration of the thyroid hormone?" He gives his opinion that the answer is in the negative, and we might add that even were it true that thyroxin acts solely as a simple catalyst accelerating oxidation, its effect on growth might well be highly complex because of alteration brought about in the efficiency of various tissues of the body.

In tadpoles Gudernatsch[32] has found that thyroid feeding definitely accelerates metamorphosis, and Allen[33] that thyroidectomy prevents it. Uhlenhuth[15], working with salamanders, obtained similar results, and more remarkable still, in the nor-

mally thyroidless Texan salamander, Typhlomolge rathbuni, which in nature undergoes no metamorphosis but remains aquatic its entire life, he could bring about metamorphosis by the administration of thyroid. "The Typhlomolge is of special interest also," he says, "because it demonstrates at what a phylogenetic stage the amphibians and perhaps the entire higher vertebrates would be if they had not developed the thyroid mechanism." He cannot believe, "that the thyroid hormone in causing metamorphosis does not produce anything new, but simply by increasing the metabolism merely accelerates a process that would occur in any case, but at a slower rate. On the contrary, even if the thyroid hormone does not do anything else but change the metabolism in a quantitative way, the Typhlomolge as well as the thyroidectomized tadpoles show that this mere quantitative change is able to create in a definite physicochemical system supplied by heredity new morphological characters that could never have developed in the absence of the thyroid mechanism."

Classification of Thyroid Disorders

With these varied and interesting facts in mind we may in true scientific spirit attempt to define and classify the ways in which the human thyroid may go astray. Classification, though essential to intelligent discussion, is by no means easy. The perfect one would be upon the treble basis of etiology, morbid anatomy and morbid physiology, and the complete diagnosis would indicate all these three in the given case. This cannot be achieved in diseases of the thyroid gland, and the classifications for the most part, which attempt it, do not add sufficient clarity to the subject to justify the strangeness of their terminology. We had best be content, therefore, with a list of simple clinical

names, being sure merely that we know precisely what we mean by them.

The thyroid contains within its capsule parenchymal cells, colloid, stroma, and blood, lymph and tissue fluid. Most of the ailments that concern us are accompanied by an increase or a decrease in one or more of these several components. Any enlargement may be called a goitre (although the term is from the Latin "guttur" which simply signifies the throat), and enlargements, theoretically at least, may be due to any of the following:

1. Increase in blood or lymph content; œdema, congestion or hæmatoma.
2. Increase in total volume of parenchymal cells; glandular hypertrophy or hyperplasia.
3. Increase of colloid stored in follicles.
4. Increase in quantity of stroma; interstitial hyperplasia.
5. Cyst formation or new growth.

An increase in one component may be offset by a decrease in another and hence no increase in total size of the gland occurs, and occasionally there may be destruction or atrophy with actual decrease in size.

The clinical entities in which these several changes may occur we shall refer to for convenience in the remainder of this work by the following well known terms: —

I. Diffuse colloid goitre { endemic / sporadic
II. Adenomatous goitre { with normal function / with hyperfunction
III. Exophthalmic goitre
IV. Cretinism { endemic / sporadic
V. Myxœdema

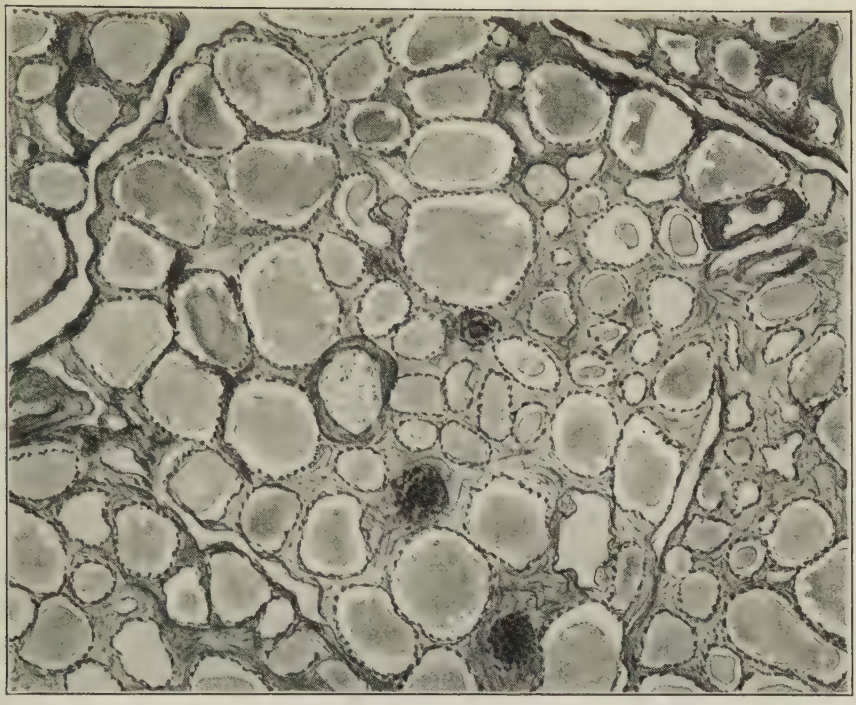

FIGURE 2. *Normal Human Thyroid.* Low power camera lucida drawing. Note especially the colloid within the lumina and the generally smooth contours of the follicular walls. Compare the amount of colloid, the size and shape of the follicles, the vascularity and amount of lymphoid tissue with the pathologic specimens shown in Figs. 6, 11, and 13.

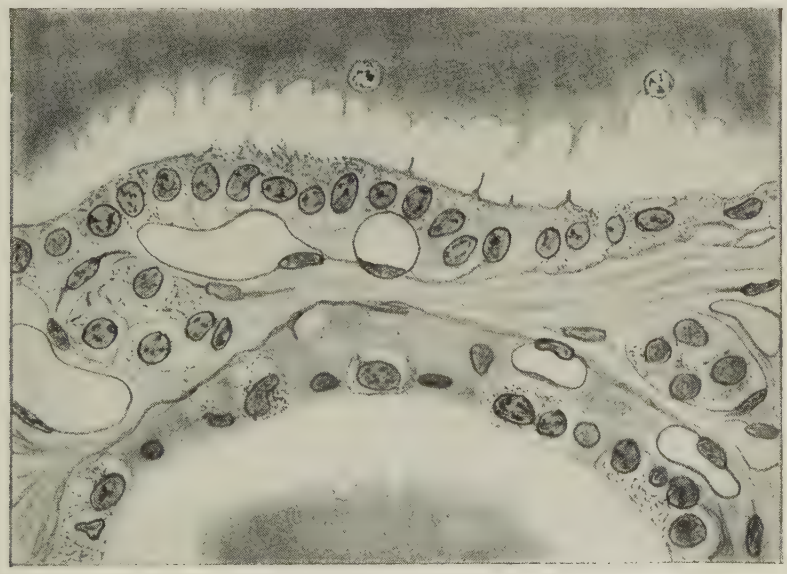

FIGURE 3. *Normal Human Thyroid.* High power camera lucida drawing. Parts of two follicles with connective tissue between. The cells of the upper follicle show granules in the cytoplasm apparently forming colloid. In the lower follicle the colloid seems to be "leaking" past a few cells to the tissue spaces outside. (After Bremer.) (Courtesy P. Blakiston Son & Co.)

VI. Cachexia strumipriva
VII. Thyroiditis
VIII. Malignant tumors of the thyroid

It will be seen that this arrangement is based in part on pathologic changes occurring in the thyroid gland, and in part on disturbance of thyroid function. From a purely functional point of view, if we leave out the inflammatory and malignant changes in the thyroid gland, thyroid abnormalities may be classed as those without significant changes in thyroid function, or simple goitre, including colloid goitre and adenomatous goitre without constitutional disturbance; those showing evidence of overactivity and consequent thyroid toxæmia, including exophthalmic goitre and adenomatous goitre with hyperthyroidism; and finally those having a deficiency in thyroid secretion, cretinism, myxœdema and cachexia strumipriva. It should be noted further that no sharp line can be drawn between colloid and adenomatous goitre from a purely clinical point of view, since the same factors apparently may act to produce both, and there is a tendency in the same individual for colloid enlargement to progress to adenomatous change. Nevertheless, with a little explanation these terms will serve our purpose, and have the virtue of being in common use.

Diffuse Colloid Goitre, as the name implies, indicates an enlargement due to increase in stored colloid. The most important factor in the endemic form is clearly a deficiency of iodine. Whether this is the only factor is open to debate. The cause of the sporadic form is unknown. Why a scarcity of iodine should lead to an increase in stored colloid is also unknown. As a rule there is no evidence of disturbance in thyroxin secretion as would be evinced by the symptoms of hypo- or hyperthyroidism, until the former appears in the second or third generation of a severe grade of the endemic form.

Adenomatous Goitre, another anatomic term, denotes a benign growth of the parenchyma with the formation of new follicles. This change occurs most frequently in endemic goitre regions in association with iodine lack, frequently in individuals who have had a pre-existing diffuse colloid goitre, and in such cases it may be considered a further reaction to this factor. For the occurrence of sporadic cases no explanation is possible. The adenomatous masses are as a rule definitely encapsulated. Since they may be made up of follicles distended with colloid, rather than those of an adult or fœtal type, there is no sharp line of separation between them and long-standing colloid goitres which show slight evidence of hyperplasia but have a nodular lobulation with encapsulation by connective tissue. For convenience we include the latter group under the general heading of adenomatous goitre. The adenomatous change taking place in the thyroid cannot be considered as invariably neoplastic in the ordinary sense, although there can be no doubt that true adenomata of the thyroid occur frequently. To the term adenomatous goitre we can add a descriptive phrase indicating whether thyroxin formation is increased; sometimes it is, sometimes it is not. The terms toxic and non-toxic are occasionally used meaning that hyperthyroid symptoms are or are not present.

Exophthalmic Goitre is purely a descriptive term but applies to a very sharply defined clinical entity probably quite distinct from any other form of thyroid disease. The etiology is unknown but the morbid anatomy is very constant, being invariably a diffuse parenchymatous hyperplasia. The nature of the functional disturbance is a matter of debate. An interesting iodine relationship occurs in this disease as in endemic goitre, but of an altogether different sort. It will be discussed in a later chapter.

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Cretinism, an ancient term derived from the French, was historically applied to the type of idiocy which we now recognize to be due simply to lack of thyroid function during the growth period. Like colloid goitre, to which it is etiologically related, it occurs in endemic and sporadic forms. It is chiefly in the cretin that we see the relation between thyroxin and growth.

Myxœdema again is a clinically descriptive term. It means simply mucous swelling, but is applied to the entire syndrome resulting in adults from underactivity of the thyroid from any cause, although sometimes the equally descriptive term cachexia strumipriva is used when the lack of function is due to surgical removal.

Thyroiditis is a perfectly sound pathologic appellation signifying an inflammation of the gland. Were this due to some specific infection the etiologic agent could be stated, as for example tuberculosis or syphilis.

Malignant Tumors of the thyroid are classified, like those arising in any part of the body, on the basis of the type of cell from which they arise. We may have carcinoma or adenocarcinoma arising from the parenchyma, or sarcoma from the stroma, or endothelioma from the vessels, or we may have metastatic growths from other tissues.

Recognition of the Several Types

Among these various types of thyroid disease certain relationships are recognized. Thus, as already stated, endemic colloid goitre hereditarily may give rise to cretinism. Exophthalmic goitre may be followed by, and may produce, myxœdema. Myxœdema may also result from thyroiditis, and cancer may develop from a benign adenoma. Furthermore,

some writers[34] insist on an etiologic difference between exophthalmic goitre and adenomatous goitre with hyperfunction. In our opinion the differences are more in degree of thyrotoxicosis and reaction pattern of patient than in cause of disease. These differences of opinion and classification may lead to confusion, but we hope by a description of the natural history of the several types of disease to make it possible to recognize these regardless of terminology.

Rôle of Basal Metabolism Determination

The essential thing, as we have attempted already to indicate, is for the physician to try to visualize the nature of the morbid process in its entirety, functional as well as structural, and etiologic when possible. The anatomy of the gland often may be guessed correctly from physical examination, its shape, contour, consistency and texture, but only can be proven by pathologic examination. Of function, however, we have an index more accurate perhaps than that in the case of any other organ in the body; we refer of course to the basal metabolism. If we are correct in assuming that the primary, probably the only, function of the thyroid is the production of thyroxin, and if the major action of this is that of a catalyst accelerating cellular oxidation, it then follows that the measurement of the rate of oxidation in the body as a whole is an index of the supply of thyroxin, and hence of the functional activity of the thyroid.

The minimal or basal metabolism of warm-blooded animals is very constant and is closely related to their size, weight and surface; to the last most closely of all. We can measure the gas exchange of a human subject and from it calculate the number of calories produced per unit of time. We can also, thanks to Du Bois and Du Bois[35] and their height-weight chart,

determine his surface area from his height and weight and calculate the number of calories he produces per unit of surface area. We can then refer this figure to the average for healthy subjects of his age and express that of the subject under study as a per cent. variation from the average for normal men, women or children.

Standard figures for the normal basal metabolism of adults have been worked out both by Benedict[36] and by Du Bois[37]. It is a matter of no great moment which ones are used, for the whole procedure is relative, not absolute. The Du Bois standards are in most general use, and since they are sufficiently accurate for clinical purposes, and since uniformity is greatly to be desired so that the work of one observer can be compared with that of another, the writers recommend their universal adoption.

The theory, principles and technique of basal metabolism determinations have been discussed abundantly and adequately in recent works by Roth[38], Du Bois[39], McCann[40], Boothby[26], Means[41], King[42], and others; to these the reader is referred. We shall be content at present with restating the conclusions reached by one of us twelve years ago[43] that,

1. Basal metabolism can be studied readily in a hospital clinic with comparatively inexpensive apparatus.

2. The normal basal metabolism is a fairly constant affair, and hence wide variations from it in disease are of interest to the clinician.

3. A marked rise occurs in hyperthyroidism.

4. A marked fall occurs in hypothyroidism.

5. In regard to hyperthyroidism it seems probable that the basal metabolism furnishes

a. The best index of the severity of the disease, and

hence is a quantitative means of following the course and of judging of the effectiveness of treatment; and

b. A valuable aid in differential diagnosis.

It seems to us now that these conclusions are still justified, except perhaps 5a, that the basal metabolism is the best index of the severity of toxic goitre, which is somewhat overstated. It is a good index, but if taken alone may be misleading.

In the chapters which follow on the several diseases, basal metabolism findings will be referred to constantly. They should be regarded as carrying about the same weight as temperature readings in typhoid or any other fever. In a dissertation upon typhoid, charts would certainly be used freely. In judging the effect of a specific remedy in an infectious disease we should regard the effect upon the temperature as important. In much the same way charts will be used in describing the progress of thyroid disorders, but the thyroid chart consists in basal metabolism, pulse, and body weight, instead of temperature, pulse and respirations, as in the ordinary bedside chart. Rates of basal metabolism will be used in judging of the effectiveness of treatment and in the differential diagnosis of obscure pictures. If always duly subordinated and correlated with the clinical data, they may properly be so employed. Du Bois[44] has well said, "God forbid that we make our diagnoses by machinery", nevertheless, if we make the machine servant of our clinical judgment it can render important aid.

To the imperfectly informed an increased rate of metabolism is often taken to be synonymous with overactivity, and a decreased with underactivity of the thyroid. We feel it our duty at the beginning of a work on thyroid disease to forestall an error of this sort.

While it is perfectly true that the administration of thyroid

or thyroxin accelerates and thyroidectomy retards total metabolism, it is by no means true that thyroxin is the sole calorigenic hormone in the body, or that all alterations in metabolic rate are dependent upon changes in its supply. It may be pointed out that even perfect thermoregulation is possible without it. The warm-blooded animal completely deprived of its thyroid becomes myxœdematous, to be sure; its body temperature falls a little and its rate of heat production falls greatly, but nevertheless it by no means becomes reptilian. The rate of metabolism in the cold-blooded animal varies with environmental temperature, and body temperature equals environmental temperature, but not so in the thyroidless mammal. Thermoregulation is preserved; heat loss is adjusted to heat production in such fashion as to preserve a fairly constant temperature, even though outside temperature may vary; this is in marked contrast to the varying temperature of the reptile or amphibian. The thyroid, therefore, is not essential to thermostasis; nor is it essential to metabolic acceleration. Marine and Lenhart[45] have shown that epinephrin exerts its calorigenic action even in the thyroidless animal.

We must not assume therefore that thyroid activity solely determines metabolic rate. We find increased metabolism in leukæmia and in fevers, sometimes in pernicious anæmia and hyperpituitarism, and we find certain persons with low rates who show no clinical evidence of hypothyroidism. It is by no means certain that in these last the thyroid gland is at fault, or that they are in any sense atypical myxœdemas as some writers would have us believe[46].

In the evaluation of our metabolism data we must preserve an open mind. An increased rate in an afebrile patient usually denotes thyrotoxicosis if leukæmia is ruled out, and if we are sure

the rate obtained was truly basal; that is to say, if the patient had not recently had food, had remained at complete rest, and was not suffering from acute emotion. Similarly, low rates almost surely denote hypothyroidism if coupled with any suggestive clinical evidence, but certain persons will exhibit them entirely without such clinical evidence and then we really do not know what they signify. These non-myxœdematous, low metabolic rate cases will be discussed more fully later on.

Symptoms of Hyper- and Hypometabolism Per Se

In order better to understand the significance of symptoms as we meet them in various clinical types of thyroid disorder, it may be well before discussing these types individually to give some consideration to the physiologic effects, and their reflection in symptomatology, of simple acceleration or depression of metabolism per se. Most of these can be foretold correctly.

An increased rate of oxidation will of necessity call for increased respiratory and circulatory activity. To meet the increased call for oxygen by the tissues, as Barcroft[47] would put it, the lungs will have to pump more air and the heart more blood. An increase in pulmonary ventilation roughly paralleling the basal metabolism can be demonstrated readily by metabolism tests on thyrotoxic patients, and observations on the minute volume of the blood flow by Davies, Meakins and Sands[48], by Liljestrand and Stenström[49], and by Bock[50] show a similar increase in circulation. The latter, involving as it does increased cardiac work, might be expected, if long continued, to produce cardiac hypertrophy; the heart having more blood to pump will undoubtedly beat at a faster rate; indeed it can be shown that a definite parallelism exists between pulse rate and metabolic rate in both toxic goitre and leukæmia, in

each of which diseases metabolism is increased. In addition to tachycardia there may, at times at least, be more blood expelled per systole, which will be reflected in an increase in the pressure of the pulse. A more forcible cardiac impulse may result, and connected with this increased circulatory activity the symptom palpitation may appear. Patients with elevated metabolisms likewise will become dyspnœic on slighter effort than normal persons, since they start with the handicap of a pulmonary ventilation already elevated even at rest.

Another group of symptoms will be traceable to the increased rate of heat loss which accompanies the increased heat production, and which serves to keep body temperature from any wide fluctuation. The channels of heat loss are evaporation of water from the skin and lungs, and radiation and conduction of heat from the surface of the body. Each of these is increased when there is hypermetabolism. The hyperpnœa will carry off more water vapor through the expired air; there will be increased sweating which increases the amount of heat lost through evaporation at the surface of the body; and there will be generalized peripheral dilatation which brings more blood near the surface where it may lose heat more readily through radiation and conduction to a cooler environment. The warm, moist skin and sensation of warmth of the hyperthyroid subject is therefore the direct result of an increased rate of heat loss.

Finally, as recognized by Müller[51], increased catabolism, unless accompanied by an equally great increase in the assimilation of food, will cause loss in body weight.

In brief then we may regard hyperpnœa, dyspnœa, tachycardia, forceful heart action, palpitation, increased pulse pressure, increased sweating, hyperæmia, sensation of warmth, loss of weight, and increased appetite as the symptoms and signs of

elevated metabolism per se. They may all occur in a normal person on the ingestion of thyroid, or in a patient with metabolism elevated for any cause. The thyrotoxic patient may have them alone, or combined with other manifestations not so easily explained.

In general the converse of all the above may be expected in persons with lowered metabolism. The ventilation indeed can be shown to be decreased, and Bock[50] has found very low blood flows in myxœdema patients. The pulse pressure tends to be low, and the symptoms connected with heat loss are reversed; decreased sweating, peripheral constriction and chilliness. The weight tends to increase. In clinical myxœdema, however, the symptomatology is dependent not only on lowered energy exchange, but also on anæmia and the effect of thyroid lack on the distribution of body fluids. As we shall see later, the intensity of the symptoms directly attributable to lowered metabolism and the exact minimal level of the metabolism bear no constant relation one to another. If, however, we bear in mind such symptoms and signs as may be taken to be the direct expression of alterations in metabolic rate, and separate them from those which are not, it will aid us in solving the individual problems in thyroid pathology as we meet them in our clinical experience. We may also trace in the clinic the effects on the human body as a whole and on its several parts of living at either an unusually high or unusually low metabolic level. We shall be surprised to find how different they occasionally are from what we might expect.

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CHAPTER III

PRINCIPLES UNDERLYING THE DIAGNOSIS AND TREATMENT OF THYROID DISEASE

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After a consideration of the development of our knowledge of the function and diseases of the thyroid gland, it is well to

discuss the general principles underlying the diagnosis and treatment of thyroid abnormalities, before taking up in detail their more prevalent forms.

Embryology and Anatomy

Embryology

In the embryo the thyroid develops from an invagination of the anterior wall of the primitive pharynx, which descends as a cellular stalk to the anterior part of the neck, and there gives rise to epithelial strands which become the thyroid gland. The connection with the pharynx, the thyroglossal tract, normally disappears, although its point of origin is recognizable in the adult as the foramen cæcum on the back of the tongue.

Developmental Anomalies

Between the situation of the thyroid gland and the foramen cæcum of the tongue, along the developmental tract of the thyroid, epithelial tissue may persist. It may be normal thyroid tissue, subject to the same changes as occur in the gland, or it may be a cavity lined with columnar ciliated or squamous epithelium, with a consequent tendency to cyst formation. The most usual variation due to this cause is a cord or band of thyroid tissue, which rarely may be double, extending upward from the isthmus toward the region of the hyoid bone, ordinarily passing to the left of the prominence of the thyroid cartilage, the so-called pyramidal lobe. This lobe may be recognized on palpation; it is obvious during thyroidectomy and should be removed if practicable, since it may produce, if subject to compensatory hypertrophy, a conspicuous deformity and recurrence.

In a similar way thyroid tissue may persist in the neighbor-

hood of the hyoid bone, or rarely as a lingual goitre at the base of the tongue in the region of the foramen cæcum. If enlarged in the latter situation, it may give rise to increasing symptoms of obstruction. The treatment necessarily then becomes surgical, but it should be remembered that the only thyroid tissue present may be abnormally placed so that ablation is followed by myxœdema.

Thyroid tissue may develop elsewhere outside of the usual situation of the thyroid. It may develop in the region lateral to the lobes, even as far out as the supraclavicular fossæ, or in the mediastinum, or in the trachea. In such instances it is spoken of as aberrant thyroid tissue. Such aberrant thyroid tissue contributes its quota to total thyroid function.

The commonest anomaly having surgical importance is cyst formation from persistence of part of the thyroglossal tract. This development probably is due to the dragging down of pharyngeal epithelium during growth of the tract, which embryologically has no lumen except at its upper part. Thyroglossal cysts occur most commonly in infancy and childhood, but may not appear until adult life. Such a cyst may become infected and rupture spontaneously, or be opened surgically. In either case, unless removal of the cyst wall has been complete, a sinus results, which may persist, or heal and discharge intermittently. Therefore, while the condition causing this sinus is congenital, the external opening is not, but once acquired it does not heal on account of persistent infection and epithelial secretions. The usual situation of such cysts, and consequently of the sinus, is in the median line between the isthmus of the thyroid and the hyoid bone, although they may occur higher. The diagnosis of thyroglossal cyst depends upon the situation and chronic character of the enlargement. If a sinus develops, it is distin-

guishable from that of cervical adenitis by its situation, and at times by the clear viscid character of the discharge. Sinuses from persistent branchial clefts may be present as such from birth, and are situated in the lateral aspects of the neck. A thyroglossal sinus is apt to rise on swallowing, and sometimes may be traced by palpation as a fibrous cord to the level of the hyoid bone. Treatment consists in complete removal of the cyst wall or sinus. In the majority of cases, the upper limit of the epithelial tract is at the level of the hyoid bone. Since occasionally the tract may extend to the foramen cæcum in extremely close relation to the hyoid bone, the surgeon to secure a permanent cure must be prepared to follow it to this level. On that account, the procedure, although a safe one, may be technically somewhat difficult. For a further discussion of this interesting anomaly, the reader is referred to papers by Bailey[1], Bertwistle and Frazer[2], Klingenstein and Colp[3], and Sistrunk[4].

Anatomy

The thyroid ordinarily consists of two lateral lobes, connected at their lower part by an isthmus which crosses the trachea below the level of the cricoid cartilage. At times junction between the two lobes is accomplished by direct fusion without a definite isthmus; rarely, connecting thyroid tissue across the trachea may be absent. The upper parts of the lobes, which extend along either side of the larynx as a roughly conical projection, reaching about the middle of the thyroid cartilage, are spoken of as the upper poles of the gland. Similarly the lower and external regions of the gland sometimes are called the lower poles, although here there is no definite projection of thyroid tissue. The gland itself is attached firmly to the

trachea and anterior part of the larynx by fibrous tissue. Since elsewhere it is only loosely attached by areolar tissue, or by vascular connections which allow some play, it rises and falls with the larynx on swallowing, a point which is of great importance in distinguishing it from other tumors of the neck. In shape it accommodates itself to that of the trachea and larynx as well as to the overlying structures, so that normally although it is relatively superficial, it is either not visible at all or else only appreciable as a slight fullness in the neck.

In discussing further the anatomy of the thyroid gland, we shall mention only those points which have a direct bearing in the examination of patients with goitre, or in understanding the terminology or effect of operative procedures and the dangers connected with this form of treatment.

The blood supply, which is extraordinarily abundant for the size of the gland, comes through two pairs of arteries, the superior and inferior. The superior are branches of the external carotid, which descend in a somewhat tortuous course to reach the superior pole of the gland, where they divide. These vessels lie in a relatively accessible and superficial position, and frequently may be palpated, the anterior branch more commonly than the main trunk, particularly in overactive and vascular glands. The inferior arteries are deeply situated and cross behind the carotid sheath from the thyroid axis to reach the posterior surface of the lower parts of the lateral lobes. There is a free communication between the superior and inferior arteries of each side but only a limited anastomosis across the median line. The main arterial and venous branches ramify upon the surface of the gland. The veins draining the upper part of the gland accompany the superior arteries; the others return independently, the lateral veins to the internal jugular,

the inferior thyroid, which are the largest, to the innominate veins. Its nerves, which are derived from the cervical sympathetic and laryngeal nerves, accompany the arteries, as do the largest lymphatic trunks.

Anatomic Relations

The thyroid gland is enveloped by a thin fibrous capsule which sends septa into the gland to produce an irregular lobulation. This capsule is not sufficiently well marked to serve as a plane of dissection during removal of the thyroid with assurance that structures posterior to it will be protected from injury. Consequently it is usual to leave with it a layer of thyroid tissue during the course of thyroidectomy. The thyroid, together with the larynx, trachea and œsophagus, lies in a compartment of the deep cervical fascia, part of which serves to provide a loosely applied external capsule for the gland. It is covered by the ribbon-like infrahyoid muscles, and the anterior margin of the sternomastoids. The carotid sheath and its contents lie posteriorly and externally, the trachea and œsophagus posteriorly and mesially. The displacement secondary to enlargement of the thyroid will be conditioned by the resistance of these structures as well as by the attachments of the thyroid, the locality of the enlargement, and the rapidity of its development. Ordinarily a slowly developing symmetrical goitre will push the sternomastoid muscle outward, coming to lie more in front of the carotid sheath, and the ribbon muscles forward, forming a prominence in the front of the neck. When the prethyroid muscles are firm and resistant, at times a surprising enlargement of the thyroid may occur without conspicuous deformity. In general, a diffuse enlargement of the thyroid may produce a large goitre, without marked pressure symptoms.

However, if the thyroid surrounds the trachea, or trachea and œsophagus, as it rarely may, constriction of these structures is likely to take place. Serious results of pressure are more common in irregular enlargements of the thyroid gland owing to the development of adenomata. The trachea may be displaced laterally by unilateral enlargement, or angulated between two adenomata at different levels. It may be compressed either laterally, or less commonly, anteroposteriorly, and this pressure if long continued may result in softening of the tracheal rings. Even a small adenoma, if confined by the firm fibrous union of the thyroid to the trachea and larynx, may cause troublesome pressure.

No anatomic structure, except the thyroid attachments, prevents descent into the superior mediastinum. Two forces, pressure of the covering muscles and thoracic aspiration, encourage advance in this direction. It is not surprising, therefore, that some irregular goitres should project into the thorax substernally, or even become completely intrathoracic. Here they may exert pressure on all structures entering the superior thoracic opening. It seems probable that adenomata developing below the point of attachment of the lobes to the trachea are most prone to progress in this direction.

Other important relations are those of the recurrent laryngeal nerves and the parathyroid glands. The recurrent laryngeal nerve runs upward in relation to the inferior thyroid artery, and ascends in the cleft between the trachea and œsophagus to enter the larynx beneath the lower border of the inferior constrictor muscles of the pharynx. It may be paralyzed by pressure or stretching due to thyroid enlargement, or by injury during the course of operation, the effects of which will be discussed later.

The parathyroid glands, usually four in number, are normally situated in two pairs, a superior and an inferior, on the posterior surface of the lateral lobes of the gland within its external capsule. The superior pair are usually to be found at the level of the cricoid cartilage, the inferior, less constant in position, near the lower edge of the gland, or perhaps below it. Although rarely less than four, they show great variation in number and position, sometimes being applied to the lateral or even the anterior aspect of the gland, or being imbedded within it, where they are in danger of surgical removal or injury. Their occasional presence at a distance from the thyroid, as at a lower level along the trachea, is of less importance, since here they are safe from interference. In shape, they are usually oval, somewhat flattened, about 4 to 6 mm. in greatest diameter, and they can be differentiated from small lymph nodes or bits of thyroid tissue by their brownish yellow color. Their blood supply usually is derived through independent twigs from the inferior thyroid or the posterior anastomotic branch between that and the superior thyroid artery. Microscopically they are clearly to be distinguished from thyroid tissue through their intercommunicating columns of epithelial cells without colloid vesicles. Surgically they are of great practical importance since their destruction results in tetany.

Methods of Examination

In examining a patient suspected of thyroid disease, we are interested in the local evidence of the goitre, in the secondary pressure effects of thyroid enlargement, in the constitutional results of thyroid toxæmia or deficiency, in the degenerative changes which develop in long-standing hyperthyroidism, and finally in any coexisting disease process. These possibilities

presuppose a thorough general examination, supplemented by such clinical and special tests as seem indicated. The only part of the examination which needs to be referred to here is that bearing more directly on thyroid disease.

Inspection

On inspection of the patient, with the neck exposed, the presence of any considerable enlargement of the thyroid becomes apparent. At times, in very thin individuals, especially if the isthmus is thick, the thyroid may be visible without enlargement, particularly on swallowing. In general, however, the presence of a visible goitre denotes some thyroid abnormality. This enlargement may be symmetrical or irregular, and may extend broadly across the neck, or project as a conspicuous deformity. Ordinarily in general enlargements of moderate size, the right lobe is somewhat larger and more conspicuous. At times there may be dilatation of the superficial veins indicating pressure on the deep venous trunks.

On inspection any signs of thyroid deficiency should be noted, such as will be described in the chapter on myxœdema. More commonly there may be evidence of thyroid toxæmia, which to the experienced observer is extremely suggestive. Nor is this entirely dependent on exophthalmos, or a staring expression and the eye signs frequently associated with these changes. A slight degree of exophthalmos may be natural in the patient, or due to some cause other than thyroid disease. It is rather an impression of emotional instability and tension, a stimulated mental attitude, expressing itself in part by conversation, in part by constant movement of a purposeful sort, the adjustment of a collar, folding and unfolding a handkerchief, or constantly recurring slight changes of position. A slight,

general flush from vasodilatation may be visible, and occasionally, an increased tendency to perspiration. Tremor may be apparent and ordinarily is best observed in the extended fingers. While loss of weight usually is obvious, occasionally thyrotoxic patients may be well nourished, or in rare instances obese. It is in the atypical cases, without eye signs and perhaps without goitre, that these appearances are particularly significant. They are essentially the signs of hypermetabolism and recognizable as such although the actual cause of the increase may remain in doubt. Other changes may be present such as flattening and recurving of the nails, or an irritated flush over bony prominences, but these are usually observable in cases otherwise well defined.

Palpation

Through palpation of the thyroid we get a better idea of its size, its shape, and its consistency. The most important determination is whether there is a general enlargement of the gland of homogeneous consistency, or whether it is a nodular or irregular enlargement. The symmetrical glands are in general colloid goitre in which the thyroid is usually soft, or exophthalmic goitre in which the thyroid is ordinarily firm and may feel even cartilaginous in consistency. Hardness in the thyroid usually indicates malignancy or chronic thyroiditis. Occasionally a general enlargement in a firm gland may feel nodular on account of slight irregularities in its surface. Another type of gland is irregular in shape, through the development of independent nodular masses, or even of a single nodule. At times these nodules may be palpated in a thyroid otherwise normal; at times the whole gland is replaced by rounded masses, sometimes alike in consistency, sometimes varying, sometimes firm

and even hard, sometimes fluctuant. In general these nodular goitres are due to the development of adenomata, and the varying consistency depends on secondary degenerative changes, more commonly necrosis and cyst formation, less usually calcification or the onset of malignancy.

A goitre is hardly likely to be mistaken for any other tumor of the neck. Its attachment to the trachea and larynx causes it to rise with them on swallowing, or at least to tip forward. Other tumors of the neck are more likely to develop laterally and to be fixed to adjacent structures. In intrathoracic goitres, barely palpable on cough, it may be a question of diagnosis between a thyroid origin and some other type of mediastinal tumor. Lateral aberrant thyroid tumors are mistaken at times for lymphoma or tuberculous adenitis or branchiogenic carcinoma.

In the palpation of goitres, fixation to the other tissues aside from the larynx and trachea is important. Ordinarily, unless the size of the goitre is too great, it may be pushed laterally as well as rising on swallowing, thus making it apparent that the muscles slide freely over it. Fixation suggests the presence of malignancy, which has broken through the thyroid capsule, or the existence of a chronic inflammatory process.

In palpating a goitre it is well to stand behind the patient and feel with the tips of the fingers of both hands. The patient may take a mouthful of water and be directed to swallow when desired. As Lahey[5] has suggested, the larynx may be displaced laterally from in front, and the lobe thus dislocated may be palpated from behind the sternomastoid between the finger tips and the thumb. When the patient swallows, a deeply situated, small adenoma may thus become readily palpable.

After the character of the goitre and its relation to surround-

ing tissue has been determined, the next point is to determine if possible any displacement of the trachea or larynx. The position of the prominence of the thyroid cartilage, and any palpable part of the trachea, such as is found occasionally at one side of the goitre or below the isthmus in thin individuals, should be determined with reference to the median line, with the patient looking directly to the front. While few direct conclusions as to pressure can be drawn, inferences as to the distribution of the thyroid enlargement are suggested. Occasionally a lateral displacement of the trachea close to the sternal notch is confirmatory evidence of an extension of the goitre through the superior thoracic aperture which otherwise may hardly be suspected. At times a large unilateral adenoma may appear on inspection as a symmetrical goitre; however, if the course of the trachea is palpable, its displacement to one side of the goitre may show the true character of the enlargement. In very large goitres, palpation of the trachea or even the larynx may be impossible.

The superior thyroid arteries, or at least their anterior branches, often may be palpable, particularly in thin individuals with exophthalmic goitre. Now that ligation is an infrequent form of treatment, the importance of this is less great than formerly. Occasionally in toxic cases a thrill in the vessel is definitely to be felt.

Auscultation

On auscultation, a bruit is commonly heard in exophthalmic goitre, rarely in other types, and consequently may be taken in general as evidence of hyperthyroidism. The bruit is usually loudest over the superior thyroid arteries, and commonly disappears after their ligation, although it may return later, a fact

which would seem to assign it definitely to this vessel, rather than to the general circulation through the gland. Occasionally auscultation may give an impression of displacement of the trachea not obtainable on palpation.

Voice Changes and Laryngoscopic Examination

The quality of the voice is important. While paralysis of one recurrent nerve is not unusual in benign enlargements of the thyroid, it usually takes place so slowly that it is compensated for by increased movement of the other cord, so that phonation is impaired only slightly or not at all. Marked aphonia is suggestive of carcinoma of the thyroid. I one cord is paralyzed, it is extremely important to know this before operation, since injury to the other side may be disastrous. This information can be obtained only by laryngeal examination, which should be a routine in all thyroid cases before and after operation. If a postoperative examination only is carried out, surgery may be blamed for a paralysis which preceded operation. If it is omitted, and only a preoperative examination made, the surgeon loses an extremely valuable check on his technic, since only direct inspection can determine surely whether or not a nerve has been impaired.

X-ray Examination

X-ray examination of the chest and lower neck is a necessary part of diagnosis. By this means only may the existence of an intrathoracic goitre be demonstrated, or the degree of substernal extension be determined. While the presence of a substernal or intrathoracic extension is unlikely in exophthalmic goitre, and most frequent in the adenomatous type, this method of examination is best used as a routine in all goitre cases,

particularly if operation is considered. Displacement or compression of the trachea may be shown. If indicated, a film of the trachea may be taken in the lateral as well as in the anterior-posterior direction, since compression or displacement may be apparent only in this plane.

Methods of Treatment

Further factors necessary for a diagnosis of the type of goitre present in an individual case, in particular variations in the basal metabolic rate, are discussed in other chapters. With this information at hand, it should be possible to outline the course to be pursued. Treatment may be directed at the size of the goitre and its local effects, such as deformity or pressure, or it may be designed to influence the function of the gland. On the whole it may be prophylactic, as in supplying an adequate amount of iodine to children and adolescents; it may be expectant, with or without medication; or destructive, the latter term embracing such measures as surgical removal, ligation, radiation, and injections, as of boiling water. These methods, preventive, medical, and destructive, all have their place in treatment of thyroid disease, which should be a co-operative enterprise with physician and surgeon both taking part. In this combination the medical man is perhaps the most important, although his form of treatment in well defined cases may not be so effective. He should have a general supervision previous to operation and determine not only any constitutional effect of thyroid abnormality but the presence of any secondary organic damage or coincident disease processes. If operation is decided on, he should supervise the preparation of the patient for this ordeal, coöperate in the after-care and keep the patient under observation after discharge from the hospital.

Destructive Measures

The prophylactic and medical forms of treatment are presented elsewhere. Here it will be sufficient to discuss in a general way the destructive measures, and particularly, to avoid repetition later, the general aspects of operations on the thyroid.

The X-ray has been the form of radiation most commonly employed in the treatment of goitre. Since it exerts a depressing influence on glandular activity, it should not be employed in the treatment of patients with simple goitres producing symptoms only through their size who have in general a normal or lowered metabolism. Not only may metabolism be depressed further, but radiation on the whole is ineffective in dealing with this type of thyroid disease. If a simple goitre demands treatment by other than medical means, it should be removed by operation. In goitre with toxæmia a depression of thyroid function is desirable. While this may be brought about occasionally by radiation, surgery is more effective. A discussion of X-ray treatment in exophthalmic goitre will be found in Chapter VI. The principal place of radiation today in the treatment of goitre is in thyroid malignancy.

Destructive injections now are used rarely in the treatment of thyroid disease, except possibly as a measure to test the patient's ability to stand operation. They were designed primarily to reduce toxicity in exophthalmic goitre, and consequently to make a subsequent thyroidectomy safer. Since a greater effect can be produced by preliminary treatment with iodine, there is now no reason for assuming the risky uncertainties and subsequent adhesions dependent on this form of treatment.

Operative Treatment

Operations on the thyroid are indicated to abolish a conspicuous deformity, to relieve pressure on important structures, particularly the air passages, to prevent the later development of serious conditions, such as hyperthyroidism and cancer, or to reduce the activity of a gland which is overstimulated. Since these conditions are present in varying degrees, it is important to have some conception of the risks of operation, the period of disability which it entails, and the likelihood of permanent ill effects. If any of these factors were serious disadvantages, we should demand conspicuous symptoms before advising operation; if not, the earlier operation is undertaken, the less its technical difficulties, and the greater the safety of the patient. It may be said that in good hands the risks of operation in non-toxic goitres are extremely slight, particularly in their early stages, far less than those of pelvic exploration in women, often so lightly advised. The mortality of operation in exophthalmic goitre, since the introduction of preliminary treatment with iodine has nearly abolished the risk of postoperative thyroid reaction, begins to approach that of simple goitre. In adenomatous goitre with hyperthyroidism, on account of its insidious onset and the associated cardiac damage, the mortality is still considerable, perhaps three per cent., but against this must be balanced the serious condition of the patient if untreated. Operations on the thyroid are well tolerated in the presence of complicating conditions, such as cardiac disease, diabetes, hypertension, and pregnancy. Anatomic damage, either to the recurrent nerves and consequently to the voice or respiration, or to the parathyroid glands, is so unusual that it hardly constitutes a real objection to surgery.

Surgical treatment sometimes is resorted to reluctantly, in the belief that a long period of time will elapse before the patient recovers fully. While this is frequently true of a laparotomy, after which, even if entirely successful, the patient is likely to regain a sense of well being slowly, perhaps only after an interval of six months or more, it is not true of thyroid operations. These patients progress rapidly to or beyond their previous efficiency. Factors in their recovery are undoubtedly the slight degree of nervous shock connected with a neck dissection, the type of anæsthesia employed, the short period of postoperative stay in the hospital, ordinarily from six to twelve days, and the shorter confinement to bed. Consequently the surgical treatment of a goitre need not be withheld through fear of a prolonged convalescence.

History of Operative Treatment. — The increasing safety of thyroid operations has been one of the most striking developments of modern surgery, the story of which has been told with masterly completeness by Halsted[6], from whom much of the following statement has been taken. The desirability of operation for goitre was obvious from the earliest times, on account of the association of a conspicuous tumor in the neck with the distressing symptoms of pressure and respiratory obstruction. Nevertheless the sporadic attempts at removal, made in Germany and Austria, France, Italy, United States, and Great Britain, were attended by such high mortality, even after the introduction of anæsthesia, that the operation generally was considered unjustifiable by the leaders of surgical opinion. While the danger feared was hæmorrhage on account of the vascularity of the gland, and many distressing deaths occurred from this cause, the actual reason for the high mortality was sepsis. The development of a systematic method of operating with control

of hæmorrhage we owe to the German, Austrian and Swiss surgeons, very little of general practical importance to the early development of thyroid surgery being contributed by the other countries mentioned.

To Billroth[7, 8, 9, 10] and his associates, and to Kocher[11, 12], principal credit is due for the unravelling of the problems associated with thyroidectomy. Of twenty early extirpations performed by Billroth[7], eight died, principally from sepsis, leading to the temporary abandonment by him of the operation. The early adoption of the principles of Lister by the German School avoided this complication. It was soon observed that total removal of the thyroid was not well tolerated. Thus Kocher [12] noted in 1883 that of eighteen out of thirty-four total extirpations reporting for examination, all but two showed symptoms of cachexia strumipriva. In a similar group of Billroth's cases, reported by Weiss[13], eight developed tetany. This led to the principle that the major portion of one lobe should be left undisturbed. The perfection of the operation of thyroidectomy we owe to Kocher, who pointed out the essential regularity of the blood supply of the gland and systematized the details of technic. A further advance was that of Mickulicz[14], who showed the possibility of cutting through the gland, a step heretofore feared, so that a portion of the lobe was left in the neighborhood of the inferior thyroid artery. The operation of subtotal thyroidectomy, to be described later, is based on this procedure, the adoption of which as a means of avoiding the parathyroid glands is due to the work of Halsted[15] and other American surgeons.

The discovery that thyroidectomy would benefit the symptoms of exophthalmic goitre was made accidentally by various observers, who operated on account of the presence of goitre

alone. The success of Kocher in operations upon simple goitres gave a great stimulus to the surgical treatment of this disease. It was soon found that a new danger, the postoperative toxic crisis, was present in exophthalmic goitre, an intensification of the toxic symptoms with rapid heart action and pyrexia, which might be fatal immediately or shortly after operation. The mortality in the hands of skilful and experienced surgeons operating upon exophthalmic goitre under general anæsthesia with as little concern as to preliminary treatment as in any tumor of the neck, approached twenty per cent., chiefly from this toxic crisis. It was soon further discovered that hemithyroidectomy, the measure formerly employed in exophthalmic goitre, although resulting in benefit, was inadequate to produce a cure. The problem then became to find a safe means of operating in this disease and to extend the operation so as to remove an adequate amount of thyroid tissue. Halsted[15] credits Kocher with the demonstration of the value of preliminary vascular ligations as a means of reducing the risk of thyroidectomy in toxic patients, although this measure had been suggested very early for the purpose of decreasing the size of large goitres. The demonstration that patients with exophthalmic goitre could be operated upon safely on a large scale by means of a series of graded operations leading up to a subtotal thyroidectomy was shown in this country by C. H. Mayo[16] and G. W. Crile[17]. The preliminary treatment with iodine of patients with exophthalmic goitre, as advocated by Plummer[18], has nearly abolished the postoperative toxic reaction, and consequently in great measure the necessity of preliminary operation.

Technic of operations. — In general operations are designed either to interfere with the circulation of the thyroid through ligations of its vessels, or to remove more or less of the glandular

tissue. These procedures may be carried out readily under local anæsthesia. Patients with goitre, particularly if toxæmic, are apt to be somewhat apprehensive, therefore general anæsthesia is perhaps preferable. Since complete relaxation is unnecessary, oxygen and nitrous oxide, or perhaps better, oxygen and ethylene, are the anæsthetics of choice. Narcosis by ether or chloroform interferes more deeply with vital processes and is consequently undesirable in toxic goitre.

For the sake of clearness in subsequent chapters, the types of operations employed in the treatment of goitre will be briefly discussed.

Ligation of vessels is planned to diminish the risk of subsequent thyroidectomy in exophthalmic goitre, and serves also as a test procedure to determine the patient's reaction to operation. It was very useful previous to discovery of the value of iodine in preparation for thyroidectomy, but is now resorted to less and less frequently. The operation is performed most readily on the superior thyroid arteries and can be carried out easily under local anæsthesia. Care should be taken to occlude the main trunk of the artery and not its anterior branch alone. The vascular bundle entering the superior pole of the gland is outlined by blunt dissection after separation of the overlying muscles and ordinarily is ligated en masse. Consequently veins, nerves and lymphatics are interrupted as well as the arterial supply, which makes doubtful what factor is actually the cause of any benefit that may ensue. When a therapeutic effect is desired, both sides are ligated, either at the same time or successively. This operation will be referred to as ligation of the superior thyroid arteries, or more briefly, superior ligation.

Ligation of the inferior thyroid arteries has been used to

secure further improvement before thyroidectomy, and is employed in some clinics as a first step in that operation. The operation is technically more difficult than ligation of the superior vessels, but the artery can be recognized as a transverse vessel coming from behind the carotid sheath at about the level of the cricoid cartilage. Even before the usefulness of iodine was demonstrated, it might be argued that patients who could undergo ligation of this artery reasonably might be expected to go through removal of one lobe, from which they would receive more direct benefit.

Operation on the thyroid itself is carried out best through a transverse incision in the line of folds of the neck, so placed that it is covered readily by a necklace or ribbon. The prethyroid muscles may or may not be divided, depending on the size and accessibility of the goitre. The simplest procedure is *enucleation of one or more adenomata or cysts* from within the substance of the gland, an operation made possible by the definite fibrous capsule which surrounds such nodules and marks them off from the remainder of the thyroid. The main vascular supply is not interfered with, and the gland after ligation of bleeding points and suture of the cavity remains essentially in its normal relations. This operation is best adapted to single nodules developing near the anterior surface of the gland and has the advantage of not exposing to injury important structures behind the thyroid lobes. It will be referred to as excision, for instance, of an adenoma.

The operation of thyroidectomy is carried out through a similar incision and demands a full exposure of the gland, or at least of the side being operated upon. A complete removal, even of one lobe, is now rarely carried out except in operating for cancer, since it not only means the possibility of destruction

of both parathyroid glands on that side, but exposes the recurrent laryngeal nerve, which is so sensitive to trauma that it is likely to be paralyzed by the dissection, even if seen and avoided. Since some thyroid tissue must be left to preserve function, that ordinarily chosen is the posterior and internal part of the lateral lobes, which serves best to protect the parathyroids and recurrent nerves from injury. The operation, therefore, is a partial thyroidectomy. If the operation removes both lobes and isthmus except for the posterior strips above mentioned, it has become customary to refer to it as a subtotal thyroidectomy, although the extent of removal varies with the surgeon, and indeed with the individual case. In general in goitres with toxæmia the best results are secured if the remaining gland tissue is as small in amount as practicable. If the partial removal is limited to one lobe, it will be referred to here for convenience as a hemithyroidectomy. The operation ordinarily is accomplished by mobilizing the gland by means of division of the superior thyroid vessels and lateral thyroid veins. The lobe then can be lifted up and turned inward exposing its outer aspect, and the proposed line of section marked out by a row of forceps which seize the superficial vascular plexus. Section of the gland itself is preceded by grasping the thyroid tissue with hæmostatic forceps, a measure which occludes the vascular branches principally derived from the inferior thyroid artery within the gland, before they retract. The important structures posterior and internal to the lobe thus are not exposed at all, unless abnormally placed.

Operative Risks

Now that the danger of a fatal postoperative reaction has been largely done away with by means of preparation

with iodine, the risks of operation become those of dissection in the thyroid area, although the patient's ability to tolerate them depends on his general condition and especially upon the degree of associated visceral damage. They are almost non-existent in early cases of adenomatous goitres, in which a simple enucleation, often unilateral, is all that is needed. They increase in cases where as complete a removal of the thyroid as possible is desirable, as in subtotal thyroidectomy for exophthalmic goitre, and are at a maximum in long-standing and neglected goitres, in particular those with substernal or intrathoracic extension. Among those risks should be counted serious hæmorrhage, air embolism, respiratory obstruction due to injury of the recurrent laryngeal nerve, the rare occurrence of tracheal collapse probably dependent chiefly upon this obstruction, menacing perhaps, but to be avoided, save in unusual instances, by a surgeon competent in this field. Operative shock is very unusual except when hæmorrhage has been great, and on this account may be combated effectively by blood transfusion.

Postoperative Complications

Hæmorrhage

While postoperative complications are infrequent, they are likely to be serious unless dealt with promptly and efficiently. Hence thyroid operations should not be performed unless there is an assistant immediately available who is able to act independently and wisely. Under these circumstances, conditions which might be fatal with delay can be checked with little harm to the patient. The least unusual occurrence is hæmorrhage during the first twelve hours or so after operation. It rarely occurs, if the patient can be made to test hæmostasis by coughing or straining just before the wound is closed. If considerable

in amount, it is treated best by anæsthetizing the patient, re-opening the wound and controlling the source, after which the wound can be closed again. A supporting transfusion, or if necessary, more than one, is desirable.

If external hæmorrhage is bad, bleeding confined in the wound is worse. The trachea may be compressed with resulting respiratory obstruction, the engorgement so produced increasing the tendency to bleed. Wide opening of the wound and evacuation of the clots may be an immediate life-saving measure.

Respiratory Obstruction

Respiratory obstruction may demand tracheotomy. It is due almost invariably to injury of the recurrent laryngeal nerves, whether by actual division or crushing, or through traction from forcible displacement of the goitre. Paralysis may be unilateral or bilateral, complete or incomplete. In incomplete paralysis, the fibres supplying the abductor muscles of the vocal cords are affected principally. On this account the affected cord remains close to the median line. If the abductor fibres are paralyzed on both sides, the rima glottidis is extremely narrow, and the cords may become opposed on inspiration. Thus, although phonation is preserved, respiratory obstruction of greater or less degree is present which may demand immediate tracheotomy as a life-saving measure. Other cases may convalesce from the operation, but are extremely and perhaps progressively handicapped by the narrowness of the chink between the vocal cords, which is insufficient for forced respiration. Such patients have a loud inspiratory stridor and are liable to suffocation, should an acute respiratory infection such as laryngitis develop. If both cords are paralyzed completely, phonation is impossible. In-

halation pneumonia may follow this injury. While the classic position for the vocal cords to assume after complete paralysis is the cadaveric, halfway between adduction and abduction and leaving a free airway, after injury from thyroid operations they tend to remain closer to the median line and may oppose on imspiration, leading to stridor or complete obstruction. A unilateral paralysis is less serious, but may lead to obstructive symptoms if accompanied by postoperative œdema of the larynx, in itself hardly likely to cause trouble. For a case report of bilateral abductor paralysis, see the end of this chapter.

Whatever the cause of laryngeal obstruction, these patients should be watched closely, even though the necessity for tracheotomy does not seem imminent. Since such patients show only respiratory difficulty, usually without cyanosis or congestion, the seriousness of the situation often is not realized. Complete obstruction and death may take place with desperate suddenness. The tendency is to postpone operation too long. Should respiration be definitely and increasingly embarrassed, the safest course is tracheotomy. Fortunately the trachea is ordinarily so exposed as a result of thyroidectomy that the insertion of a tube ordinarily can be carried out rapidly and bloodlessly after opening the wound.

A unilateral paralysis, if it does not cause immediate trouble, is likely to be entirely compensated for. The unaffected cord swings across the median line and thus opposes the other cord, so that phonation is preserved, although the power of the voice may be somewhat impaired. In fact the majority of these lesions is likely to escape detection, unless a routine postoperative examination of the larynx is carried out. Injury to the superior laryngeal nerve is infrequent and without serious

consequence, although it may disturb the sensory mechanism of the larynx, so that choking on swallowing occurs during convalescence, or may lead to slight relaxation of the vocal cords with consequent coarsening of the voice. In our experience, there has been only one case of bilateral abductor paralysis, reported herewith, and three per cent. of unilateral paralyses, as shown by laryngeal examination.

Pulmonary Complications

Pulmonary complications, such as pneumonia, have been infrequent in our experience, showing an incidence less than after simple laparotomies. On the occasions when such infection develops, the patient is likely to be much reduced by a long-standing thyrotoxicosis, or else to have suffered some form of injury to the laryngeal nerves causing malfunction of the larynx. Pulmonary embolism is a possibility, but fortunately is rare. Slight degrees of pulmonary collapse are common. Rather careful chest examination is necessary to find them. This complication usually clears rapidly.

Sepsis

Following thyroidectomy, particularly in toxic cases, the temperature rise commonly occurring after any aseptic operation is more marked and persists longer, even if a definite postoperative reaction does not occur. On this account the appearance of the clinical chart is not a good guide as to the presence or absence of sepsis. We have found a definite pyogenic infection leading to breaking down of the wound very unusual, although a few cases show a diffuse infiltration and redness of the skin flaps, which ordinarily subside spontaneously and may be due in part to tissue damage caused by the operation. If

the drainage tract persists, as is likely when a dead space is left following the removal of a large goitre, infection may take place during subsequent dressings, and is troublesome rather than serious. If the trachea is opened, either purposely or accidentally, an extensive wound infection develops.

Tetany

Tetany is a possible postoperative complication, in spite of precautions taken to avoid injury to the parathyroids. It is most likely to follow removal of both lobes of the thyroid for exophthalmic goitre, when the remaining gland tissue may be very small in amount, but may occur after a subtotal removal in adenomatous goitre, and even has been reported after unilateral operations. The actual mechanism of production of tetany is usually in doubt. There may be no discoverable parathyroid tissue removed with the gland at the time of operation. It is probable, therefore, that injury to the parathyroids either through interference with their blood supply, operative trauma, or subsequent sepsis, is more a factor than actual removal of the glandules at the time of operation, a view which is strengthened by the transitory nature of the symptoms in many cases. Nevertheless, as Lahey[19] has suggested, it is well to examine as a routine the specimens removed at operation, and if any tissue suggesting parathyroid is found, to transplant it into the sternomastoid muscle, preferably reserving a bit for microscopic examination.

Ten cases of tetany are known to have developed following thyroidectomy at the Massachusetts General Hospital. These were not all permanent. Symptoms have developed from one to four days after operation. Of these ten cases, two were fatal, one during the first generalized spasm, the other, reported by

C. A. Porter[20], after two months and three weeks. The tetany was temporary in the majority of the remainder. One of the patients showed remarkable and persistent choreiform movements and was considered to have possibly a psychoneurosis. However, she showed on these occasions definite tetanic spasms, the excitability of her muscles to galvanic stimulation was definitely increased, and her blood calcium 5.56 mg. per 100 c.c. on the twelfth day gradually increased to 8.5 mg. four weeks after operation, when she was apparently relieved. In this case occasional spasms recurred for a month later, after which she seemed to be entirely well. The case histories of two patients with tetany are reported at the end of this chapter.

A well-marked case of tetany with the characteristic carpopedal spasm (flexion of the wrist, flexion of the fingers with extension beyond the metacarpophalangeal joints, plantar flexion of the feet, with flexion of the toes) can hardly be mistaken for anything else. But the essential thing is to make the diagnosis as early as possible in order to institute treatment. On this account prodromal symptoms are extremely important, although they may be absent in individual cases. Suggestive symptoms are paræsthesia in the extremities, particularly numbness and tingling, muscular twitchings, radiating pain, and a sense of lassitude or of vague indefinable distress. Crile[21] has described circum-oral pallor as early evidence of this disorder. At the least suspicion of tetany, an effort should be made to confirm or disprove the diagnosis by attempting to bring out the characteristic signs of the disease.

The most useful clinical sign is perhaps Trousseau's, the production of the characteristic spasm in an extremity by pressure on its nerve trunks. In practice it is sufficient to en-

circle the arm from its flexor aspect with the thumb and fingers, exciting moderate pressure, or a light tourniquet may be applied sufficiently tightly to cause venous congestion. Since latent tetany may exist, it is best to make use of this sign as a daily postoperative routine during the convalescent period. Chvostek's sign, contraction of muscles by percussion of the nerve supply, is best brought out by tapping the trunk of the facial nerve. It is sometimes positive in the absence of tetany. Increased electrical excitability of the muscles (Erb's sign) is extremely valuable as a confirmatory test. It requires, however, special apparatus and experience, and is more difficult to apply at the bedside. Serum calcium is diminished and may be reduced to 4 or 5 mg. per 100 c.c. of blood, from a normal of about 10; and serum phosphorus is increased to 6 to 10 mg. from a normal of 4 to 4.5 mg. The distinctive spasms are likely to be fugitive and are easily overlooked. Even when well marked, they are intermittent with periods of complete freedom. While in most instances they are limited to the extremities, extension to the trunk and face may occur, as well as involvement of the laryngeal muscles leading to respiratory obstruction. Occasionally generalized convulsions may develop during which death may take place. After one attack patients are likely to be extremely apprehensive, so that marked excitability or neurotic symptoms may complicate the picture. Rarely a definite psychosis may develop. Periods of hyperpnœa frequently are to be observed. The course may be rapidly and progressively fatal, although it is probable that this result would be avoided in the acute phase with the treatment now at hand, providing diagnosis is made early. In other cases the condition may be temporary with complete restoration to normal, or latent without the development of character-

istic spasms, a deficiency extremely likely to pass unrecognized.

Occasionally the disease may become chronic and persist for years without tendency to improvement. These patients, while free as a rule from obvious manifestations of tetany, show a persistently low serum calcium and are likely to have definite spasms brought on by anything making a further demand on calcium metabolism, such as pregnancy, or lactation, or by many other less explainable causes, such as menstruation, infections and gastro-intestinal upsets, or in fact, for no obvious reason. They show more or less chronic invalidism, which is accentuated by nervousness or mental depression. Lens opacities are frequent and tissue changes somewhat suggestive of myxœdema have been observed. One extremely interesting case reported by Aub[22] was operated on for double cataract twenty weeks after thyroidectomy and was treated for asthma for seven years before the true condition was discovered.

In the treatment of tetany the principal indication is to raise the blood calcium. This can be done in the following ways.

1. High calcium diet, i.e., add 10 c.c. of a 30 per cent. solution of anhydrous calcium chloride or 15 gm. of calcium lactate to the diet. In urgent cases calcium gluconate, 10 c.c. of a 10 per cent. solution, may be given intravenously.

2. Low phosphorus diet, i.e., avoid milk, cheese, nuts, chocolate and bran.

3. Acidosis, which may be produced by calcium chloride or by ammonium chloride.

4. Dihydrotachysterol, or "A.T.10", a substance lying chemically between vitamin B and parathyroid hormone, has been found very satisfactory in the treatment of parathyroid

tetany. It must be used with caution lest it produce hypercalcemia. It has a delayed action. The usual dose is 3 c.c. per day, by mouth, for five days and then 3 to 6 c.c. per week for maintenance.

5. Thyroid hormone. Aub and his coworkers[40] have shown that thyroid definitely raises the level of blood calcium. Since many patients with tetany have an associated low metabolism or have had too much thyroid tissue removed, the use of thyroid in these is doubly useful.

Permanent Ill Effects of Operation

While most of the complications of the postoperative period are entirely recovered from, a very few patients may show permanent ill effects from this operation. All cases necessarily carry a scar, but in the majority of instances this is inconspicuous and frequently almost invisible. Occasionally adhesion to the trachea causes it to rise on swallowing, but this fixation tends to disappear in time. Such slight defects are readily corrected by a minor plastic operation under local anæsthesia, provided the incision is originally well placed, and the best evidence that they are not of serious moment is that a request for correction is almost never made.

Myxœdema is a possibility following subtotal thyroidectomy, but is so unusual and comes on so late after operation, as to make it more probable that it is due to a progressive change in the thyroid tissue itself, than that it is an effect of surgery. In any case, provided it is recognized and the patient appreciates the necessity for treatment, it is corrected so readily by the continued use of thyroid, that it hardly constitutes a serious disadvantage. In fact, as between a residual toxæmia due to insufficient removal of the thyroid in exophthalmic goitre and

a myxœdema, the advantages are with the patient in the latter state.

The serious ill effects, fortunately rare, have to do with operative injury to the structures behind the thyroid lobes, the parathyroid glands and recurrent laryngeal nerves. Chronic tetany has already been spoken of, a most distressing and disabling condition, likely to result fatally unless treated vigorously.

Bilateral laryngeal paralysis with respiratory obstruction, in the cases where spontaneous recovery does not take place, is almost equally serious. While these cases can get on indefinitely with a permanent tracheotomy, it is a serious handicap. Jackson[38] has devised an operation to increase the air space available for respiration by means of punch excision of one vocal cord. Anastomosis of the cut inferior laryngeal nerve to the descending branch of the hypoglossal, with return of function, has been accomplished by Frazier[39], who reports about 66 per cent. of favorable results in 10 patients. The advantages are all with the latter type of operation, if it can be performed successfully.

Illustrative Cases

Some of the complications of thyroid surgery are illustrated by the cases which follow.

Case No. 1013. *Exophthalmic Goitre: Postoperative Toxic Reaction Before the Use of Lugol's Solution.*

History and Examination. — A man of 35, married, a watchman for a lumber company, entered the hospital May 11, 1921, complaining of weakness on exertion, trembling of his hands and frequent attacks of palpitation for the past two years.

Examination. — This showed a marked, firm, symmetrical enlargement of the thyroid, exophthalmos, somewhat enlarged heart, and tremor of fingers. His pulse varied from 100 to 120. The basal metabolic rate was

plus 88 per cent. A consultant found congenital heart disease with patent ductus arteriosus. This condition, however, did not seem to affect the efficiency of the heart. His thyroid toxæmia appeared well tolerated, and he was believed to be in much better condition than his metabolic condition suggested.

Management. — He improved somewhat with rest in bed for a week. He was difficult to manage and was extremely dissatisfied with the prospect of a series of operations. It was decided to ligate only the right superior pole of the gland, but under anæsthesia the patient's condition seemed so satisfactory that a right hemithyroidectomy was carried out. He returned to the ward in good condition, with a pulse rate of 110. During the day he showed progressive increase in temperature and pulse rate, the temperature rising to 106° F. and the pulse to 160. He became extremely delirious. During the night he showed some improvement. During the next day, however, he was irrational and the temperature rose again to 105° F. and the pulse rate increased to 160, being at times 200. The restlessness and delirium were succeeded by unconsciousness. The patient died 38 hours after operation. Treatment was essentially without effect. It consisted of ice bags to precordia, neck and axillæ, subcutaneous saline infusions, water and glucose solutions by rectum, morphia and bromides in large doses and digifolin. There was no autopsy.

Case No. 1120. *Exophthalmic Goitre: Bilateral Abductor Paralysis Necessitating Tracheotomy*

History and Examination. — A woman of 39 entered the hospital Sept. 16, 1921, with a five year history of thyroid enlargement, having for three months symptoms of increased nervousness, loss of weight, palpitation and dyspnœa on exertion.

Examination. — This showed the characteristic findings of exophthalmic goitre and auricular fibrillation which was confirmed by the electrocardiogram. The basal metabolic rate was plus 54 per cent.

Management. — The patient improved considerably after ligation of the superior poles, and returned for a subtotal thyroidectomy which was done eight weeks later under gas oxygen anæsthesia. Laryngeal examination previous to this operation was not recorded. At the completion of the removal of the right lobe a respiratory stridor was noted. After removal of the left lobe obstruction was greater and the patient became slightly cyanotic. Shortly after her return to the ward the difficulty in breathing became alarming. The wound which had begun to bleed on account of venous congestion was reopened and a tracheotomy was done

without anæsthesia. Her respiration became quiet and bleeding ceased. Following this she made a satisfactory recovery aside from sepsis in the wound. Examination of the vocal cords showed both cords almost fixed in the median position leaving a very small chink between them. The diagnosis was bilateral abductor paralysis. The patient was discharged wearing a tracheotomy tube. Six months later she came back feeling well aside from her respiratory condition. She had gained weight and was doing well with regard to her thyroid toxæmia. Her tracheotomy tube had been removed two weeks previously, and since then she had had increasing difficulty in respiration with severe choking sensations. Examination showed the old tracheotomy sinus contracted down, but still open. While asleep she had a loud inspiratory stridor which disturbed the whole ward.

Under local anæsthesia the whole sinus was excised, the opening in the trachea enlarged and a tube inserted. A year later she came in to the Massachusetts Eye and Ear Infirmary for removal of the tube under observation. Examination at that time showed complete abductor paralysis of the right cord, while the left paralysis had nearly disappeared, the cord having practically normal motion. The tracheotomy tube was removed and the patient suffered no discomfort or dyspnœa. Thirteen months later the patient wrote that she was doing well and gaining weight. At times she still had a choking sensation.

Case No. 1584. *Exophthalmic Goitre: Tetany Following the Last of a Series of Graded Operations; Recovery; Gradual Relief from Tetanic Symptoms*

History and Examination. — A married woman of 40 entered the hospital on July 25, 1922, with a history of illness for two and a half years, beginning with nervous excitability and tremor, followed successively by exophthalmos, goitre, tachycardia and palpitation, these symptoms persisting in spite of rest. Her metabolic rate was plus 56 per cent. with a pulse rate of 106. She was considered to have exophthalmic goitre of moderate severity, and a program of graded operations was decided on.

Management. — A double superior ligation was performed July 31, 1922. In October she showed no symptomatic improvement; she had gained no weight, and her metabolism was plus 70 per cent. with a pulse rate of 126. On this account the operation was limited to a right partial thyroidectomy, although her condition under anæsthesia suggested that more might be accomplished safely. Following this procedure she showed marked improvement, as evidenced after seven months by a gain of 6 kilos

in weight, a pulse of 80, and a metabolic rate of plus 15 per cent. She still had, however, palpitation and shortness of breath, and appeared to be more thyrotoxic than her metabolism indicated. In May, 1923, the remaining lobe was partially removed, the operation being without incident. A considerable portion of both lobes, about one-sixth, had been left to protect the parathyroids. There was very little postoperative reaction. On the morning of the next day the patient showed tetanic contraction of the fingers. In the afternoon Chvostek's sign was positive. She was given calcium lactate gr.xx (1.3 gm.), t.i.d. The following day the signs of tetany had nearly disappeared. On the fourth day, following the omission of the calcium lactate, the tetany became more severe, with carpopedal spasms. She was given 10 c.c. of 25 per cent. magnesium sulphate intramuscularly, her calcium lactate was increased to gr.xl (2.6 gm.), t.i.d., fluids were forced, and proteins were restricted in her diet. Following this she showed a normal progress from her operation, without definite tetanic spasms. She did have, however, a persistent Chvostek's sign, increased electric excitability of the muscles, a sense of weakness in her arms and legs with occasional cramps and twitchings, and a feeling of numbness in her finger tips. After discharge occasional slight tetanic spasms occurred until September, and then disappeared. In February, 1924, she had gained 20 kilos, her pulse was 68, and her metabolism plus 9 per cent. Her hyperthyroidism appeared to be completely controlled although her exophthalmos persisted.

Case No. 3140. *Exophthalmic Goitre: Acute Tetany Following Subtotal Thyroidectomy*

History and Examination. — A woman of 30 entered the hospital on March 3, 1925, with a history of exophthalmos of eight months' duration, followed by a goitre, loss of weight, marked perspiration, and mental irritability. For four months previous to entry she received treatment for tertiary syphilis, including iodine.

Management. — Following admission she was prepared for operation for ten days with Lugol's solution. The basal metabolic rate showed a drop from plus 52 per cent. to plus 22 per cent. A subtotal thyroidectomy was advised irrespective of the syphilitic condition which seemed to have no bearing on the operative recovery.

She went smoothly through the operation and immediate postoperative recovery until the fourth day when a house officer observed cramping of the fingers with associated symptoms of numbness and tingling during the removal of the skin clips. While conscious of the importance of this

finding, he did not report it directly to those in charge of the patient, believing that it was generally known. Consequently the treatment was not modified. She remained apparently well until the morning of the seventh day when she had a severe attack of tetany with carpopedal spasm. She was given calcium lactate by mouth, glucose 10 per cent. by rectum, with triple bromides. During the administration of calcium chloride intravenously she went into a convulsion, became cyanotic, and died in spite of restorative measures. A partial autopsy (limited to the thorax, without removal of organs) showed status lymphaticus, the thymus weighing 35 grams, œdema of the lungs, slight chronic pleuritis, and a question of slight syphilitic aortitis. No parathyroid tissue was recognized in the wound.

Comment. — In this case there was an interval between the observed symptoms of tetany and the fatal convulsion which might have been employed effectively in treatment. A routine attempt to bring out Trousseau's sign would have led to an early diagnosis of tetany, and consequently to the application of measures which might have averted disaster.

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CHAPTER IV

COLLOID GOITRE

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It is appropriate to start a dissertation upon diseases of the thyroid with a discussion of colloid goitre, for the reason that it is both the commonest malady involving the gland in question and, except for cachexia strumipriva, perhaps the best understood in the manner of its causation. As the name implies, the enlargement is due to an increase in the quantity of colloid stored within the follicles, and this in the fully developed stage is the only essential variation from the normal, although Marine has found in animals that this stage is preceded by a parenchymatous hyperplasia[1].

Diagnosis

The diagnosis of this type of goitre depends upon the appearance and feel of the gland and upon the absence of symptoms or signs of hyperthyroidism. The enlargement is symmetrical or nearly symmetrical, and in the uncomplicated type has a smooth surface and even consistency, the latter being rather

FIGURE 4. *Colloid Goitre.* Wax reconstruction of the follicular lumina by G E. Wilson. Compare with Figs. 1 and 10.

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soft and elastic in the earlier cases, and firm or even hard in the long-standing ones. Usually there is no evidence on physical examination of increased vascularity, although sometimes in the very long-standing cases the veins over the gland may be markedly engorged, and in rare instances a bruit may be heard. The goitre is never tender or inflamed nor adherent to any surrounding tissues, except the trachea, its normal attachment.

Because of the lack of evidence of disturbed thyroid function and of the eye signs of exophthalmic goitre, the disease is often called simple goitre, and because of its tendency to develop at or before puberty it has been labelled adolescent goitre. These terms, like colloid goitre, are purely descriptive; it is merely necessary for the practitioner to remember that they are synonymous.

The most striking aspect of colloid goitre is its geographic distribution. In certain regions the incidence of goitre is very high, occasionally so high that practically the entire population is affected. Such regions are said to be goitrous, and in them goitre is endemic. While it is probable that in these regions thyroid enlargement begins almost universally as colloid goitre, usually at puberty or during adolescence, further changes take place in the thyroid gland leading to the development of irregular or nodular areas of hyperplasia, and to the formation of adenomata. Consequently in adults it is unusual to find the persistence of a pure colloid type of goitre; the majority show to a greater or less degree a nodular adenomatous change. From a clinical point of view this is important, since the adenomatous goitre gives rise to a variety of secondary changes, as will be discussed. In an endemic goitre region, therefore, we should expect a prevalence of colloid goitre during adoles-

cence, a predominence of adenomatous goitre without hyperthyroidism during early adult life, and the occurrence of secondary changes such as hyperthyroidism or malignant degeneration during middle life or later. Indeed on account of the latter, Coller and Barker[2] go so far as to speak of endemic goitre as a precancerous lesion. Further, if the goitrous condition persists through two or three generations or longer, endemic cretinism may occur. Curiously enough, the distribution of exophthalmic goitre seems unaffected by the presence of endemic goitre.

FIGURE 5. *Goitre Map of the United States.* Goitre rate per 1000 drafted men in the United States. (After McClendon and Williams.)

The distribution of goitrous districts in the United States is shown in Fig. 5. Sometimes goitrous areas are very sharply demarcated, being perhaps a single small valley. In general it may be said that the regions that are goitrous are geologically either mountainous or old glacial areas. In nearly all of the great mountainous regions of the world colloid goitre is endemic, the Alps and Himalayas for example. Also, in our

great lake district and in the lake districts of Norway and Sweden we find colloid goitre endemic in what was once the seat of an ice field.

The incidence and severity of endemic colloid goitre vary in different goitrous districts. Some districts are mildly goitrous and others markedly so. Berkshire County, Mass., has been shown by Bigelow, Aub and Sisco[3] to be an instance of the former; the environs of Lake Erie have long been known as an example of the latter.

Colloid goitre occurs occasionally, however, in absolutely non-goitrous districts, and under these circumstances may be called sporadic.

Etiology and Pathology

The cause of endemic goitre long has been considered to be in some way connected with drinking water. In Switzerland it was believed that the drinking of water from melted snow was responsible, while other writers have thought that there is a water-borne infecting agent.

The work of Marine[4, 5, 6, 7] and his associates, however, renders it close to certain that colloid goitre is a result of absolute or relative lack of iodine, iodine starvation; it is in a sense a deficiency disease. Many studies have been made of the relation between natural iodine supply and the incidence of endemic goitre. The findings of McClendon and Williams[8] for the United States are shown in Fig. 5, and a summary of goitre surveys in the several states will be found in the paper of Olesen[9]. Also of interest are such observations, as those of von Fellenberg[10], who found in four localities in Switzerland the following relationships between the concentration of iodine in rock and soil and the incidence of endemic goitre.

Location	Per cent. goitre	Iodine in rock	Iodine in soil
Effingen	1.	5400	11900
Hornussen	12.1	830	4940
Hunzenschwil	56.2	510	620
Kaisten	61.6	430	1400

The deficiency of iodine, Marine points out, conceivably may be brought about in three different ways: first, by any factors which increase the demand for the iodine containing hormone, e.g., puberty, pregnancy, lactation, the menopause, infections and intoxications; second, by any factors which interfere with the absorption or utilization of the normal intake of iodine; and third, through actual deficiency in total iodine intake.

Marine believes that the parenchymal cells of the thyroid undergo regularly first hypertrophy then hyperplasia whenever the iodine store falls below a given level (less than 0.1 per cent. in the animals studied), and that these two processes continue until exhaustion, atrophy, or recovery supervenes. Recovery occurs only when iodine is given, and it is not recovery in the sense of a return to a normal sized gland, but merely an involution on the part of the parenchymal cells to their normal state. Apparently during the hypertrophy stage an increased quantity of colloid is formed, which is poor in iodine[4, 11, 12]. If iodine is then given, the thyroid rapidly accumulates it, having an extraordinary affinity for this element, as Marine has shown. Upon resaturation with iodine involution of the parenchyma takes place, but not disappearance of the colloid. The colloid goitre remains, so Marine believes, but the gland is in a normal status so far as its functional capacity is concerned. On the other hand, if iodine is not supplied, parenchymal atrophy is the

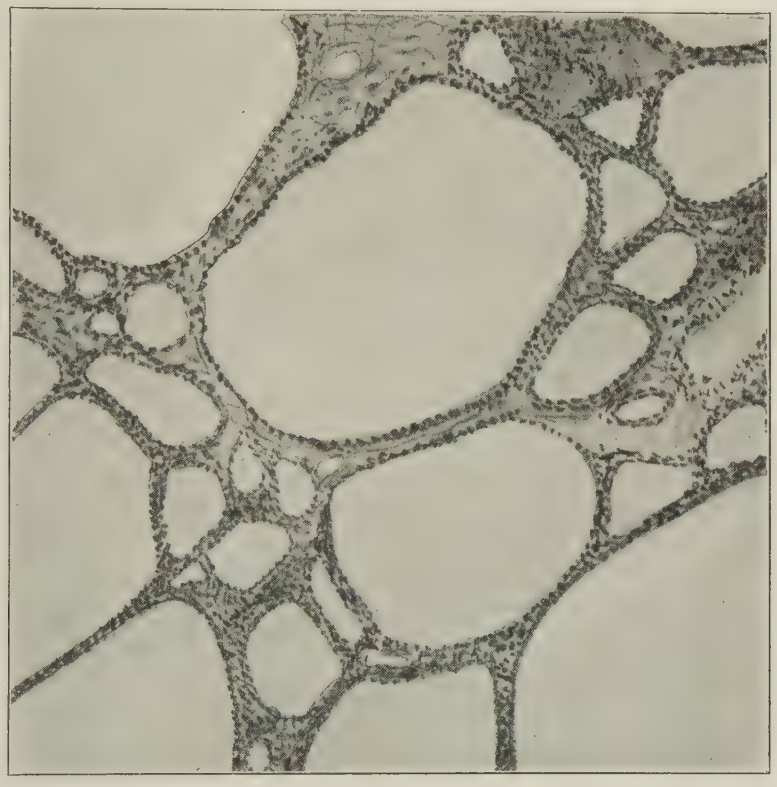

FIGURE 6. *Colloid Goitre.* Low power camera lucida drawing. Compare the size of follicles and total quantity of colloid with that of the normal gland shown in Fig. 2.

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end result, and after this has occurred restoration to a normal functional status through the administration of iodine is no longer possible. Marine's experimental work further shows that these changes which produce colloid goitre will not take place if the thyroid is kept saturated with iodine.

Of Marine's facts there can hardly be any doubt; his data are voluminous and consistent, and show precisely the same changes and iodine relationships in all species studied, man, sheep and dog. Furthermore, his main conclusion that colloid goitre, or as he prefers to call it, simple goitre, is essentially the resultant of iodine deficiency seems abundantly justified, particularly in view of the fact that with Kimball[13] he was able to show that in a goitrous district (Akron, Ohio) the prophylactic use of iodine will prevent the development of simple goitre in school children.

There are some aspects of the matter, however, that are by no means clear. If, as Marine supposes, atrophy of the gland is the pathologic end result of iodine starvation, why do we not get myxœdema as the invariable clinical end result in all cases where iodine is not supplied subsequently? That such is not the case is obvious; in any goitrous district great numbers of persons live a normal life span with well marked colloid goitres, and have none whatever of the constitutional signs of disturbed thyroid function.

Unless we are fundamentally wrong in our conception of the function of thyroxin, there cannot be an actual deficiency in thyroxin manufacture without a drop in energy exchange; yet the experience of many observers has been that in large series of cases of colloid goitre no constant variation in basal metabolism occurs. Sometimes slight elevations are found, sometimes slight depressions, but for the most part the metabolism falls within the zone commonly called normal.

One is led to believe, therefore, that even in highly goitrous districts the lack of iodine is relative, not absolute. Enough is actually obtained at all times to provide the necessary, or nearly necessary, quantity of thyroxin, but because of its relative scarcity the thyroid gland, though ultimately successful in supplying the demand for the hormone, is forced to labor unduly in the process, and the hyperplasia is the expression of this strain. It is possible to believe that the extraction of a sufficient quantity of iodine for the elaboration of a normal quantity of thyroxin might involve a greater amount of work on the part of the thyroid cells when the concentration of iodine is unusually low in the blood, and also a greater circulation of blood through the gland.

The periods of growth of the goitre in the endemic regions, as Marine emphasizes, are during those times when metabolic activity is increased, puberty, pregnancy and infection. It is true that energy exchange at these times actually is somewhat increased. Perhaps had an organism none of these periods of hypermetabolism to go through, there would be no development of colloid goitre, even in an endemic goitre region.

Marine's conception involves the assumption that colloid, once accumulated, cannot be got rid of, and that the larger colloid goitres are due to a series of cycles of hypertrophy, hyperplasia and involution, each one causing some permanent enlargement; that is to say, the increase takes place by steps, as for example after repeated pregnancies.

Just why colloid once formed should be irremovable is not clear. As has been pointed out earlier, there is some reason to believe that colloid is being formed constantly. Furthermore, colloid goitres do get smaller under certain circumstances, both spontaneously and occasionally after the therapeutic use of iodine, or of dried thyroid gland.

The Akron experiment of Marine and Kimball[13] and the experience of Klinger[14] in goitre prophylaxis in Switzerland ought to be enough to convince the most skeptical of the fundamental deficiency nature of the disease. Nevertheless, that the relationship between external iodine supply and goitre incidence is by no means always constant, and that other factors may play a part, is shown even by the work of Marine[15] himself, at least in respect to trout.

Several writers have been impressed with the apparent importance of contamination of drinking water in goitre incidence. McCarrison[16], for example, who has studied the problem very exhaustively in India over a fourteen year period, has become so convinced of an infectious origin of endemic goitre that he defines it in the following words "a chronic infectious disease occurring in more or less circumscribed areas and characterized by a non-inflammatory and progressive enlargement of the thyroid gland, which is unattended by marked functional disturbances".

Other writers have been impressed with the great variation in goitre incidence among neighboring villages, which is seemingly inexplicable on the basis of any difference in environmental iodine supply, and have concluded that water pollution must play a part. Blacklock[17] had such an experience in Sierre Leone and regarded the contamination of drinking water with human or animal excreta as an important factor in rendering it goitriferous. He does not believe, however, as does McCarrison, that this signifies an infectious origin of the disease, for, as in the case of Marine and Lenhart's trout, iodine still will act as a prophylactic. The mechanism, Blacklock thinks, is rather to be found in some interference in iodine absorption or availability brought about in some way as yet unknown, by the influence

of the contaminating agents, or in some increase in iodine need which these agents may produce through their action on the organism.

The work of the last decade (since 1928) indicates that bizarre locality differences in the incidence of simple goitre are due to the presence of certain goitrigenic principles in food. Certain lots of cabbage were shown to be goitrigenous in rabbits by Chesney, Clawson and Webster[24], and Marine and his coworkers[25,26] have shown that this action is dependent on the presence of certain cyanide compounds. Cabbage goitre is in fact cyanide goitre, and the mechanism for this type of goitre seems to be that the thyroid gland responds to the oxidation inhibiting action of cyanide by undergoing hyperplasia. It is significant, however, that an excess of iodine will prevent cyanide or cabbage goitre, showing that in the last analysis these types of goitre also are to be regarded as iodine-want goitres.

The Course and Sequellæ of Endemic Goitre

The course and sequellæ of endemic goitre are of vital interest to the physician. In one sense the ailment may be regarded as merely the exaggeration of a normal state. For example, a slight increase in the size of the thyroid at the time of puberty in girls and during pregnancy is too frequent to be regarded as pathologic, but it is at these times that colloid goitre most commonly makes its appearance. Both endemic and sporadic colloid goitre occur much more frequently in the female than in the male sex, the ratio being anywhere from eight to about three in women to one in men. In the most goitrous districts, as the incidence of goitre approaches the total population, the difference in incidence between the sexes de-

clines. This fact has been used as an argument against the simple iodine deficiency theory of the disease, but it seems to the writers that it is not necessarily detrimental to that view. It is entirely possible that the demand for functional activity on the part of the thyroid differs in the two sexes, or that other endocrine factors may influence the availability or effectiveness of the thyroid secretions in a different way in the female from in the male. Very little is known, for example, of the interrelation of ovary and thyroid, and until such information is at hand, it seems idle to dismiss the overwhelming evidence in favor of the iodine starvation theory, because it provides no obvious explanation for the sexual difference. Furthermore Marine[7] states that in the lower animals this sex difference has not been demonstrated.

Perhaps the most usual story in either endemic or sporadic goitre is that the gland appeared enlarged for the first time in a girl at the establishment of the catamenia, in a boy at the age of fourteen or fifteen, and that it slowly increased in size for a few years, then either assumed a stationary size or perhaps even got slowly smaller. Another type in its mode of onset is the congenital goitre[18]. That will be discussed later in connection with cretinism. Still a third type is that where no enlargement is noted until pregnancy, when a definite fullness appears and persists. In either the first or last type succeeding pregnancies may be followed by further enlargement. Colloid goitre may appear at puberty or during pregnancy in either goitrous or non-goitrous districts. Congenital goitre is for the most part endemic. Sporadic congenital goitre is exceedingly rare. Talbot[19], for example, tells us that he has encountered it but once. This was in the case of twins both possessing moderate sized goitres at birth. The father and mother and six older children

were entirely free from thyroid abnormalities, and the family lived and the babies were born in a non-goitrous district. The goitres were nearly symmetrical, smooth and firm. There were no eye signs or any hyperthyroid manifestations. The metabolism of one was determined at seven days of age and of both at two and one-half months. All these results were within normal limits.

The symptoms of colloid goitre may be said to be non-existent. Perhaps a better way to put it is that there are no essential symptoms of colloid goitre nor physical signs beyond the goitre itself. When symptoms are present, they are due to some added factor and not exclusively to the colloid gland per se. For example there may be symptoms due to pressure upon some of the cervical structures. This is particularly likely to happen when the goitre dips down into the thorax. Purely cervical goitres, regardless of their size, are relatively unlikely to produce pressure.

Symptoms of over- or underfunction of the thyroid, that is to say of thyrotoxicosis or myxœdema, occasionally may be present but they form no essential part of the disease. A person with colloid goitre for example may develop myxœdema in the same way as one not previously goitrous, or he may develop exophthalmic or adenomatous goitre followed by hyperfunction. It is probable that, if an organism ever did live in an environment completely free from iodine, eventually the functional state of complete athyroidism would supervene. It would be impossible to escape that outcome unless an active thyroid hormone could be made without iodine, but all evidence is against that. It is probable, however, that a totally iodine-free environment is never encountered actually.

Simple colloid accumulation in either the endemic or spo-

radic form seldom gives rise to a goitre of more than moderate size. Continuation of growth resulting in a large sized goitre is due invariably to the formation of adenomatous tissue and cystic degeneration. In both goitrous and non-goitrous districts enormous non-toxic goitres are seen. These undoubtedly started as simple colloid goitres, but on section they will always show adenomata and numerous various-sized cysts, the latter being due to follicular distension possibly with fusion of adjacent follicles, or to the breakdown of adenomatous nodules from hæmorrhage or from aseptic necrosis.

Sudden increase in size of the thyroid may be due to hæmorrhage into a cyst. When such an occurrence takes place in a midline cyst situated well down beneath the sternum, acute pressure symptoms may result. Adenomata are also of importance on account of the possibility of pressure, and further because they may cause hyperthyroidism or become malignant.

Sporadic Colloid Goitre

Symptomatically and morphologically identical with endemic goitre, the sporadic variety is of obscure origin. Simple colloid goitres of fair size are met with not infrequently in non-goitrous districts and in the offspring of non-goitrous mothers, chiefly in adolescents. If they appear at puberty, they may either disappear or persist. The rôle of iodine is doubtful. Occasionally some reduction in size will follow iodine therapy; more often it will not, at least that has been the experience in our clinic. If these goitres are due to iodine lack, it must be because of some error in assimilation, for living as these patients do in non-goitrous regions, there can be no question of an insufficient intake of that element. It has been suggested by McCarrison[16] that intestinal bacteria or parasites might prevent the absorption of an otherwise adequate intake.

Prophylaxis of Endemic Goitre

If the disease is due to deficiency of iodine, prophylaxis obviously consists in supplying that substance; the debatable points are dosage and method of administration. Two general principles have been used: one of wholesale iodinization of the entire community in goitrous districts either by putting iodine in the town water supply, or by the general sale of iodinized table salt; the other that of giving iodine not to the whole population but only to school children under puberty and to pregnant and lactating women. Man is apt to get into dietary difficulties the more civilized he becomes, and among others is that, whereas old-fashioned sea and natural deposit salt contained plenty of iodine, modern pure table salt contains little or none.

The method of preventing endemic goitre by iodinizing the public water supply is the least popular; it is generally regarded as wasteful and uncertain, so probably will not be widely used. The general use of iodinized table salt, on the other hand, has its adherents as well as its enemies. The argument generally raised against it is that, while it undoubtedly will be effective in preventing simple goitre in young persons, it will also precipitate thyrotoxicosis in certain older ones who have adenomatous goitre[20, 21, 22].

To throw light on this disputed subject Kimball[23] analyzed a series of cases in Cleveland. Of a total of 2659 patients with thyrotoxicosis there were 309 (11.6 per cent.) whose story suggested that iodine might have been a causative factor. Of these 309, in 6 (2 per cent.) iodinized table salt, in 37 (12 per cent.) iodine medication not prescribed by a physician, and in 266 (86 per cent.) iodine medication prescribed by a doctor seemed responsible.

Therefore, although the risk from iodinized salt apparently is slight, we still should stand with those who prefer prophylaxis by the administration of iodine tablets to children and pregnant and lactating women, to the iodinization of the whole community through salt.

The consensus of opinion now seems to be that for prevention 10 mg. per week will suffice. This can be given in tablet form, several such being upon the market.

Marine[7] concludes a recent discourse on goitre prevention with the following words which are well worthy of repetition, "Simple goiter is the easiest and cheapest of all known diseases to prevent and its control may be accomplished by available methods as soon as organized society determines to make the effort. The prevention of goiter will mean a great deal more than eliminating this form of cervical deformity. It means in addition the control of those forms of physical and mental degeneracy such as cretinism, mutism and idiocy, which are dependent upon thyroid insufficiency."

Treatment of Colloid Goitre

If prevention is easy, treatment, on the other hand, is not. Iodine may be tried, but its curative action is by no means as certain as its preventive, and if used in too large dosage it may, as stated before, prove dangerous. In both the endemic and sporadic types slightly larger doses will be necessary for treatment than for prophylaxis. In young adults 20 to 30 mg. per week in any convenient form may be tried. Larger doses should be avoided, particularly if any nodules can be felt in the thyroid. The older the patient and the older the goitre the less the likelihood of reduction. In cases of long standing, which have proved resistent to iodine, particularly if metabolic rate is at all

depressed, thyroid can be tried cautiously. One or one and a half grains (0.065 to 0.1 gm.) a day is quite enough with which to start, and the patient should be closely observed during its use.

A diffuse colloid goitre is unlikely to require operative removal. When goitres require surgery simply on account of their size, they generally have progressed beyond the stage of diffuse colloid goitre, and have developed a nodular structure due to adenomatous change or to degenerative cysts. This generally will be the case in goitres persisting in persons over twenty-five years of age. The discussion of the surgical treatment of these latter conditions will be presented in Chapter VII. Here it is sufficient to say that there is no objection to operating on a diffuse colloid goitre, if its size produces trouble in the way of deformity, pressure or appearance. Other indications for removal are unlikely. In general, since the metabolism is within normal limits, a considerable amount of thyroid tissue needs to be left to maintain function. The enlargement of a diffuse colloid goitre is usually bilateral, therefore a partial removal of both lobes and isthmus is indicated to preserve the symmetry of the neck. The amount of tissue remaining after operation should approximate in size the normal thyroid.

Illustrative Cases

Three cases illustrating the type of colloid goitre seen in a non-goitrous district, and the results of treatment therein, follow.

Case No. 4035. *Sporadic Colloid (Adolescent or Simple) Goitre Developing at Puberty: Getting Smaller on Thyroid, Larger On Iodine*

History and Examination. — A girl of fifteen years, native of a seashore town in Massachusetts, was first seen June 10, 1926. Ten months before she had experienced her first catamenia, and six months before

had noted for the first time a fullness in the neck which since had been increasing in extent. There had been no constitutional symptoms of any kind save easy fatiguability, and no local pressure or other manifestations. Her parents and five younger siblings were well, none of them having or having had goitre. A moderate sized swelling of the thyroid involving both lobes and isthmus was observed. The right lobe was somewhat larger than the left and the whole gland was soft and elastic; no lumps were felt. A systolic bruit was audible over the entire organ. There were no eye signs and no tremor. The heart sounds were loud and rapid, but the heart was not enlarged and there were no murmurs. The basal metabolism was quite normal. The neck measured $13\frac{3}{8}$ inches.

Management. — A diagnosis of sporadic colloid (adolescent) goitre was made, and thyroid in small doses was ordered, with the results shown in the following table.

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
June 10, '26	− 3	112	45.3	Neck $13\frac{1}{8}$ in.
" 29, '26	− 4	84	43.4	Thyroid gr. iss (0.1 gm.) daily since last note.
July 29, '26	+ 5	84	43.5	Thyroid gr. iss (0.1 gm.) continued. Goitre smaller. Neck $12\frac{1}{4}$ in. Feels very well.
Sept. 25, '26	−10	96	45.6	Thyroid gr. iss (0.1 gm.) since last note; omitted. Neck $12\frac{1}{2}$ in.
Dec. 31, '26	− 7	76	49.3	Potassium iodide gr. v (0.3 gm.) daily since last note. Goitre distinctly larger. Neck 14 in. Loud bruit.
Feb. 5, '27	− 5	78	47.3	Potassium iodide gr. v (0.3 gm.) and thyroid gr. iss (0.1 gm.) daily since last note; former omitted. Goitre smaller. Bruit gone.
May 7, '27	− 5	88	47.0	Thyroid gr. iss (0.1 gm.) since last note. Goitre smaller. No bruit. Feels well. Neck 13 in.
Nov. 19, '27	+ 2	84	51.2	Thyroid gr. iss (0.1 gm.) since last note; omitted. Feels very well. Goitre barely palpable. Neck $12\frac{3}{8}$ in.

Comment. — This case represents well the simple colloid goitre of adolescence, coming on at puberty for no known reason in a child of healthy parents in a non-goitrous district. At no time was there any clear cut evidence of hyper- or hypothyroidism. Under small doses of thyroid, which she tolerated without consistent change in metabolism, pulse or weight, the goitre got definitely smaller, and her general health improved.

It is of distinct interest to note that when potassium iodide was substituted for thyroid the goitre got bigger. This was undoubtedly due to accumulation of colloid, not parenchymatous hyperplasia, for there was no coincident symptom of hyperfunction or rise in metabolism. When thyroid again was given along with the potassium iodide the goitre again got smaller, and finally nearly disappeared.

The bruit is of some interest, for this case shows that these sounds are not found solely in toxic goitre. It increased definitely with the enlargement during potassium iodide medication, indicating that circulation may be increased during periods of active colloid storage as in that of increased thyroxin manufacture. It disappeared as the gland receded under thyroid.

This case represents fairly our usual experience with goitres of this type; namely, that although iodine is of great value in the prevention of endemic goitre, often it is of but little use in the treatment of already established colloid goitre. Thyroid in small doses is more effective, and if the dose is regulated carefully can be given without producing clinical hyperthyroidism.

Case No. 3644. *Sporadic Colloid (Adolescent) Goitre Decreasing Under Thyroid*

History and Examination. — A Jewish girl of fourteen, born in Boston, of healthy parents, was first seen on November 25, 1920 complaining of enlargement in the neck. The thyroid was found diffusely and moderately enlarged, smooth, soft and non-tender, without thrill or bruit. There were no symptoms or signs of thyrotoxicosis and no eye signs. The swelling had appeared first one year before and had grown progressively larger to date. She had begun to menstruate two years before. Her general health was perfectly good and her development normal.

Management. — A diagnosis of sporadic colloid (adolescent) goitre was made and thyroid ordered as shown below.

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
Nov. 20, '25	−11	92	51.9	Neck 13 in.
Dec. 5, '25	− 9	82	53.1	Thyroid gr. iss (0.1 gm.) daily since last note. Neck 13 in.
Jan. 13, '26	− 5	76	54.7	Thyroid gr. iss (0.1 gm.) daily since last note. Neck $12\frac{7}{8}$ in.
Feb. 13, '26	+ 5	84	56.2	Thyroid gr. iii (0.2 gm.) daily since last note. Neck 13 in. Feels very well.
Mar. 13, '26	− 2	68	55.3	Thyroid dosage same.
Apr. 10, '26	+ 3	64	55.7	Thyroid same. Neck $12\frac{5}{8}$ in.
Jun. 12, '26	− 3	78	50.4	Thyroid same. Neck $12\frac{5}{8}$ in.
Jul. 9, '26	−13	85	51.7	Thyroid same. Goitre smaller. Neck $12\frac{1}{8}$ in. Feels very well.
Sept. 13, '26	− 5	86	51.7	Goitre just palpable. Neck $12\frac{1}{2}$ in. Thyroid gr. iii (0.2 gm.) since last note. Says she feels somewhat nervous.
Nov. 15, '26	−10	69	52.1	Neck 12 in. Thyroid gr. iii (0.2 gm.) since last note; omitted. Potassium iodide gr. v (0.3 gm.) daily since last note. Less nervous.
Feb. 4, '27	−13	64	51.9	Potassium iodide gr. v (0.3 gm.) daily since last note. Neck $12\frac{1}{2}$ in. Feels very well, not nervous.
Jul. 16, '27	−17	72	50.9	Goitre barely palpable. Potassium iodide gr. v (0.3 gm.) daily since last note.

Comment. — Like Case No. 4035 this represents the ordinary type of sporadic colloid (adolescent) goitre developing in a girl at puberty. Here too there was improvement under thyroid in small doses, but no subsequent enlargement under potassium iodide. Some slight subjective nervousness without other evidence of hyperthyroidism disappeared under the iodide, but not necessarily because of it.

CASE NO. 4559. *Sporadic Colloid Goitre Developing in a Man at Twenty-one Years Going Down Under Thyroid*

History and Examination. — An American truck driver of twenty-one, born in Vermont, presented himself on February 16, 1927 with a moderate sized symmetrical goitre which he had noted first two years before, and which had increased slowly in size during that time. There were no nervous or circulatory symptoms, but the goitre, he said, was beginning to choke him. The goitre was firm and smooth, somewhat behind the sternum and clavicles, but X-ray showed nothing within the thorax. He tired easily and felt dopey at times but had had no chilliness. A sister recently had had an operation for toxic goitre.

Management. — A diagnosis of sporadic colloid goitre was made and thyroid ordered. The results were as follows:

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
Mar. 2, '27	+ 4	60	76.8	Neck $15\frac{5}{8}$ in.
May 2, '27	+13	72	75.0	Thyroid gr. iss (0.1 gm.) daily since last note. Neck 16 in. More strength. No thyrotoxic symptoms.
Jun. 28, '27	+10	64	73.3	Thyroid gr. iss (0.1 gm.) daily since last note. Goitre softer with occasional firm nodules.
Nov. 14, '27	+19	72	72.5	Thyroid gr. iss (0.1 gm.) daily since last note. Goitre smaller. Neck $14\frac{3}{4}$ in. Feels very well.

Comment. — This case shows that sporadic colloid goitre is not peculiar to women. The reduction in size under thyroid was definite, and satisfactory to the patient. Some evidence of a constitutional effect of the hormone is afforded by slight loss of weight and increased metabolism. But there were no unpleasant symptoms of hyperthyroidism; instead his strength was improved, and no tachycardia developed.

The finding of nodules as the goitre softened is of interest; these probably represent adenomatous foci, and may in later life enlarge and

give rise to thyrotoxicosis either spontaneously or following the administration of iodine, which consequently should be employed, if at all, only with extreme caution. Malignant degeneration also is a possibility later in life.

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CHAPTER V

EXOPHTHALMIC GOITRE

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Diagnosis

The diagnosis of this disease depends upon recognition of its cardinal symptoms and signs. In its fully developed form it is perhaps the easiest diagnosis in the whole field of medicine to make correctly. A layman or even a child can make it. To enlarge upon the more usual manifestations would be an insult to the medical reader's intelligence. It will suffice merely to recall the famous Merseburg triad: goitre, exophthalmos, and increased heart action, and Marie's fourth sign, tremor.

The point that should be emphasized chiefly is that the symptoms and signs of exophthalmic goitre are those of simple hyperthyroidism, as for example those following thyroid ingestion by a normal person, plus some others. These others are the eye signs and certain nervous and mental disturbances

which seem to belong to this form of thyroid disease alone. The simple hyperthyroid symptoms, as we have pointed out in an earlier chapter, are chiefly those directly or indirectly due to increased metabolism and the resulting increased circulation and respiration, namely, those due to increased heat loss, increased sweating, peripheral dilatation, flushed warm skin, sensation of warmth; those due to increased destruction of tissue, loss of weight and, in compensation, increased appetite; those dependent on increased circulation, palpitation, dyspnœa, tachycardia, increased pulse pressure, and violent heart action with apparent enlargement of the heart and systolic murmurs; and finally those due to a mild increase in irritability of the central nervous system.

The purely exophthalmic goitre or Graves' manifestations have to do with the nervous system, probably both central and vegetative, and of these the group of eye signs is at once the most striking and perhaps the most obscure, striking in appearance, obscure in origin. The signs are the protruding globe of Parry, Graves, and Basedow, the wide fissure of Stellwag, the lid lag of von Gräfe, the poor convergence of Mœbius, and the infrequent winking of Dalrymple. Any or all of these signs may be present, and in some undoubtedly true case of Graves' disease none may be; this last, however, is a rare occurrence. Neither the significance nor the manner of causation of these eye signs individually or collectively is known. It is suspected that the exophthalmos is caused in some way by overactivity of the sympathetic nervous system; recall for example, Cannon's[2] production of it by fusing the phrenic and sympathetic nerves. But how this sympathetic excitation forces the globe out remains a mystery. A spasm of Müller's muscle has been suggested, and engorgement of the vessels behind the eyeball. The deposit of fat undoubtedly occurs in

long-standing cases, but it is more probably an effect than a cause of exophthalmos, for exophthalmos may develop in a few days. The lid lag probably is independent of the exophthalmos and due to a hyperactivity of the sympathetic innervation of the levator palpebræ. The lid is drawn back farther than normal and fails to follow the globe in downward rotation. It helps to give the appearance of fright and stare that these patients have. The poor convergence (Mœbius' sign) may be merely a part of the general myasthenia, the weakness showing first in the most difficult coördinating movement. Both lid lag and exophthalmos are met occasionally in persons showing no evidence of thyroid disease.

Exophthalmos has been produced in animals by the administration of thyrotropic hormone of the anterior pituitary gland. Indeed Marine and Rosen have produced it in thyroidectomized animals[52]. This independence of the eye signs from the other characteristics of the disease, which are more directly related to excess of circulating thyroid hormone, has been suspected on clinical grounds. Thyroid feeding does not induce exophthalmos.

The presence of eye signs often is dissociated clinically from the degree of thyroid intoxication. Examples of the latter are (1) the persistence of eye signs following relief of thyrotoxicosis after subtotal thyroidectomy, (2) progression of exophthalmos despite relief from thyroid intoxication and (3) presence of eye signs in cases of myxœdema supervening on the untreated course of thyrotoxicosis (see Case No. 13,481 in Chapt. V). We have been struck by the frequency with which patients at the Massachusetts General Hospital presenting progressive exophthalmos have low metabolic rates.

The eye signs of Graves' disease are seen occasionally in

hypertension, leukemia, chronic nephritis and in maniacal patients, who do not have exophthalmic goitre. Asthmatic and ulcerative colitis cases may show them as well.

We favor the view that, whether or not an individual patient develops eye signs, depends on the presence or absence of certain vestigial smooth muscles in the orbit, which under conditions of sensitized sympathetic stimulation are capable of producing propulsion of the eye ball in the presence of the generalized weakness of the striated musculature which exists in the disease. This muscular weakness and wasting in some cases may be so marked that in certain instances of exophthalmic goitre the mistaken diagnosis of progressive muscular atrophy has been made.

Eye changes and symptoms may be the first or sole manifestations early in the disease and may antedate the development of an increased metabolic rate. Unilateral exophthalmos may occur, and inequality of degree of exophthalmos in individual patients is noted quite frequently. In remission, exophthalmos may be the only residual sign of the disease demonstrable.

The other peculiar Graves' symptoms are the extreme restlessness amounting to almost ceaseless motion and the mental excitation which Müller[3], and later Plummer[4], has compared to that of intoxication with alcohol, or (Müller) lead or iodine. These manifestations in Graves' disease seem to be more marked than anything occurring in simple hyperthyroidism. W. A. Plummer[5] also stresses the myasthenia as a characteristic feature, and in examining patients notes especially the performance of the act of climbing upon a chair or table, the thyrotoxic individual showing definite myasthenia in performing this act. Similarly Lahey[6] measures the time that the seated

patient can hold the leg extended at right angles to the trunk. The hyperthyroid individual cannot do so for more than thirty seconds, whereas the normal person can do so for a minute.

A number of other manifestations occur occasionally, for example, diarrhœa and amenorrhœa, but these among thyroid diseases are by no means peculiar to exophthalmic goitre. Slight fever is present occasionally when the intoxication is marked, and high temperatures may be met in toxic crisis. The increase in pulse rate[7] and pulse pressure[8] closely parallels the rate of metabolism. The blood often shows a relative lymphocytosis[9], the so-called Kocher blood picture, but this is by no means constant.

Of laboratory tests, other than basal metabolism determination, having diagnostic value, little need be said. The reaction to adrenalin is increased, and this fact has been used by Goetsch[10] as a diagnostic criterion. It is inferior in this respect to basal metabolism and is not without the possibility of serious discomfort to the patient. Sugar tolerance is decreased[11, 12, 13], the curve following glucose ingestion showing a higher peak than is seen in normal persons, but this again is more of physiologic than of clinical interest. The vital capacity of the lungs has been found by Rabinowitch[14] to show a reduction which closely parallels the rise in metabolism.

Hertz and Lerman[53] studied the blood picture in 30 cases of exophthalmic goitre by the supravital technique and found that relative and absolute monocytosis, endothelial leucocytosis, are far more characteristic of the disease than is lymphocytosis. The blood formula was changed by iodide administration in the direction of a decrease of the percentage and absolute numbers of monocytes.

Blood cholesterol determinations were found to be lower in

thyrotoxic than in normal individuals. Our experience does not justify our using the blood cholesterol as an aid in diagnosis. Determinations of it by the Bloor method in cases of frank thyrotoxicosis have ranged from 97 to 240 mgm. per cent.

Impedance angle determinations have been claimed to be of diagnostic aid in thyroid disorders. Horton, VanRavenswaay, Hertz and Thorne[54] published results of a clinical evaluation of impedance angle determinations in thyrotoxicosis and myxœdema and concluded that they were of no clinical value and certainly did not supplant the basal metabolic rate as a measure of thyroid function.

Blood iodine determinations may be used as confirmation of a diagnosis of toxic goitre. A discussion of this aspect follows later in connection with iodine metabolism studies in the disease.

The relative frequency of the various characteristic symptoms and signs, when the disease occurs in a non-goitrous region such as Boston, may be observed in the following group of the last one hundred and fifty unselected consecutive cases at the Massachusetts General Hospital.

Nervous instability	occurred	in	100	per	cent.
Tachycardia	"	"	99	"	"
Tremor	"	"	98	"	"
Goitre	"	"	94	"	"
Palpitation	"	"	91	"	"
Loss of weight	"	"	84	"	"
Exophthalmos	"	"	83	"	"
Dyspnœa	"	"	81	"	"
Thyroid bruit	"	"	81	"	"
Asthenia	"	"	81	"	"
Increased sweating	"	"	78	"	"

Increased appetite	occurred	in	66	per	cent.
von Gräfe's sign	"	"	63	"	"
Mœbius' sign	"	"	35	"	"
Diarrhœa	"	"	29	"	"
Pressure symptoms	"	"	25	"	"

There are very few diseases having such a constant symptomatology as this, and very few, therefore, in which the diagnosis is simpler. The presence of the Merseburg triad justifies a positive diagnosis practically always, and the existence of any four of the first thirteen of the manifestations listed above should arouse strong suspicion of thyrotoxicosis.

It might be asked what criteria were actually used in this series of one hundred and fifty in making the diagnosis of exophthalmic goitre, since it appears that not all possessed the Merseburg triad, six per cent. having no goitre and seventeen per cent. no exophthalmos. We should reply that it was made upon the presence of three or more of the above symptoms or signs combined with a persistent elevation of basal metabolism, and the exclusion of other possible causes therefor. It is a matter of common experience, for example, that the picture of Graves' disease occasionally is met complete in every way save that there is no palpable or visible goitre, but in such cases the gland histologically shows the customary hyperplasia. In a like manner all other signs and symptoms may be present save the eye signs, again with typical histology in the gland. In other words, the diagnosis is a clinical one, hence an impression only, depending on no one factor. Certain features usually present may be lacking in the given case, though we may point out that in this series of one hundred and fifty patients suffering from what we considered to be Graves' disease or exophthalmic goitre, there were none who did not exhibit increased nervous

irritability and increased metabolic rate, and only one without tachycardia. It would be risky to make the diagnosis in the absence of any of these, though their presence might be explainable on bases other than thyrotoxicosis. It would also be risky to make it in the absence of both goitre and eye signs, though no doubt such cases occur. Nor can we say that exophthalmic goitre is impossible without tachycardia and hypermetabolism. Cases of typical exophthalmic goitre are found in children with normal basal metabolism, and lately W. O. and P. K. Thompson[15], in the Massachusetts General Hospital clinic, have called attention to undoubted Graves' symptoms in certain long-standing cases which at the time were exhibiting normal metabolic rates. The explanation of the latter will be discussed later.

Tachycardia too might be absent in thyrotoxicosis provided some counteracting factor producing bradycardia coexisted, as for example heart block. One of the earliest cases studied in our laboratory[16] was thought by her own physician to have myxœdema, because of lethargy and bradycardia. Accordingly he had given large doses of thyroid which had had no effect upon pulse rate. Electrocardiogram, however, showed the auricular rate to be 119 and the metabolism was plus 41 per cent. She was thyrotoxic but had a slow pulse because she had a complete disassociation of auricles and ventricles.

Finally we have nowadays, thanks to Plummer[17], in addition to the characteristic symptoms and signs and elevated metabolism, a characteristic response to large doses of iodine which occurs with sufficient regularity in true Graves' disease to constitute a diagnostic test of great importance. This reaction, consisting in a prompt fall in metabolism and pulse rates and marked amelioration in the nervous phenomena under the

action of the drug, will be considered further under etiology and treatment.

Differential Diagnosis

The differential diagnosis of exophthalmic goitre is chiefly from other sorts of thyroid disorder, colloid and adenomatous goitre and from functional diseases of the nervous system, cardiac[18] and other neuroses which may imitate its symptoms. Chronic febrile states, particularly tuberculosis[19, 20] may resemble it, as may also leukæmia, in which, as we pointed out earlier, basal metabolism is elevated. Colloid goitre usually should offer no difficulty in differential diagnosis, for of all the manifestations of Graves' disease, the goitre alone would be present, but occasionally it may be accompanied by marked neurotic symptoms which might cause it to be mistaken for thyrotoxicosis. Adenomatous goitre with hyperthyroidism easily might be mistaken for exophthalmic goitre; indeed several writers deny that it exists as a separate entity[21,22]. We are inclined to agree with Plummer[23] and others[24, 25] that it does, but the arguments on both sides will be presented later (see Chapter VII).

In distinguishing between the neuroses and Graves' disease the basal metabolism is of the utmost value, it usually being possible in the former to obtain ultimately a reading within ten per cent. of the standard figure. Nervous persons often show an elevation at the first, and perhaps even at the second and third tests, but finally after they have become accustomed to the technic their rates fall to a normal level. The elevations on the earlier occasions are probably adrenal reactions. Our rule is, in cases where the symptoms of Graves' disease are suggestive only, and where the basal metabolic rate is determined for

differential diagnosis, to repeat the test until a level constant on different days is obtained. In contrast to the truly thyrotoxic person who without treatment will show a maintained elevation, the neurotic shows a rate falling with each successive test until the normal zone is reached.

The exclusion of leukæmia should be easy, if no positive evidence of that condition is found in the blood, spleen, and lymph nodes. The metabolism here is of no value in the differential diagnosis as it is elevated in both conditions. Tuberculosis occasionally offers trouble, but really should not, for beyond loss of weight and tachycardia there is little similarity in symptomatology. Tuberculosis if febrile may be accompanied by a slight elevation of metabolism, but for a given pulse rate it would be distinctly less than that found in exophthalmic goitre (see Chapter II).

Clinical Course

The impression seems strong in the minds of most writers that what may be termed psychic traumata, such as fear, sorrow, rage, play an important rôle in the production of this disease. Nearly anyone who has seen a considerable number of these cases can recall certain patients in whom the complete picture apparently developed in a day or two after some experience causing intense emotion (as in Case No. 3947). Since in a greater number, however, no such factor appears to exist, one must confess that the rôle of nervous shock is veiled in mystery; nor as we study the past histories of these patients does any other factor stand out as probably of importance etiologically. In the previously mentioned series of one hundred and fifty cases the circumstances of the onset of toxic symptoms were as follows:

Definite history of psychic trauma	37	cases
Onset after an acute infection	11	"
Strain or overwork	6	"
During pregnancy *	10	"
After childbirth *	10	"
At puberty	2	"
At menopause *	9	"
Preceded by non-toxic goitre	12	"
Coming on for no apparent cause during good health	53	"

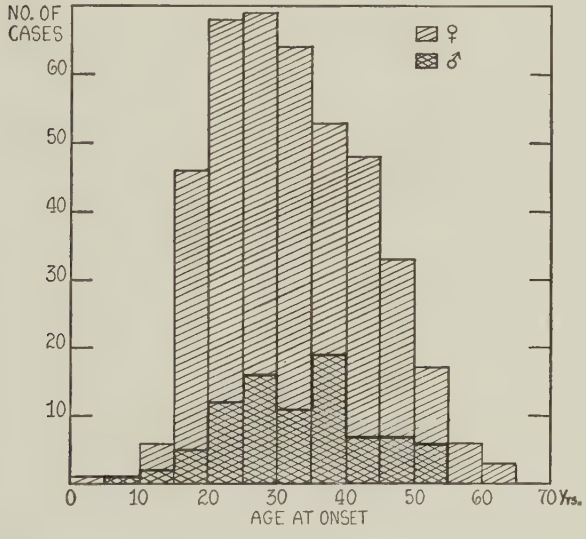

FIGURE 7. *Exophthalmic Goitre.* Age distribution curve in a non-goitrous territory, 500 Massachusetts General Hospital cases.

There is therefore no one factor that in any convincing way appears to be causative; several, very likely, are contributory to the onset of symptoms. Were fright alone capable of precipitating this syndrome, it certainly would be more common in soldiers, for example, who have been under fire, or after civilian disasters of one sort or another. Its greater frequency in women

* 120 women in the series.

is of distinct interest. In our series of one hundred and fifty there were thirty males, and this is similar to the experience of others. Yet there is no striking association of its onset with any of the critical periods; puberty, pregnancy or menopause, in the sex life of the female as in the case of colloid goitre. In fact the distribution curve for age at onset shows the peak at thirty-one to thirty-five years, which coincides neither with puberty

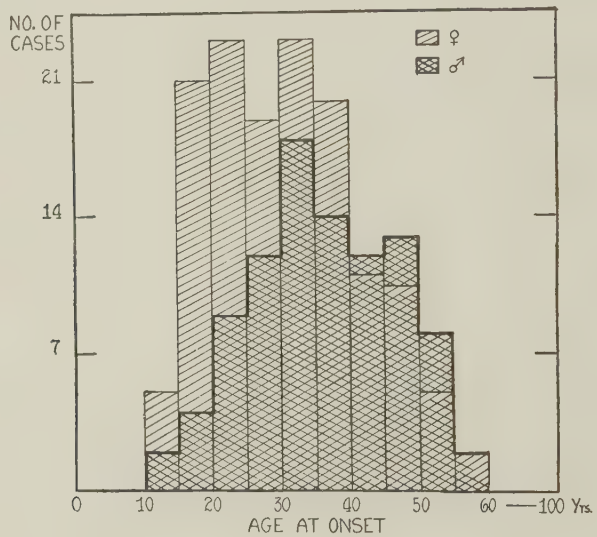

FIGURE 8. *Exophthalmic Goitre.* Age distribution curve in a goitrous territory, 233 cases from the University Hospital, Ann Arbor, Mich. (Kindness of Dr. Mark Falcon-Lesses.)

nor the menopause (see Figs. 7, 8 and 9). It should be noted, too, that all thyroid diseases, not simply exophthalmic goitre, are more frequent in women than in men.

The onset even when traceable to no recognizable provocative factor is often abrupt. Furthermore, it is the rule for the various classic phenomena, goitre, eye signs, and thyrotoxic symptoms, to appear at approximately the same time. This is a point of some value in the differentiation from adenomatous

goitre, in which the goitre usually precedes the toxic symptoms. In some cases, on the other hand, the onset is insidious, and occasionally only one or two of the typical symptoms are complained of.

The course of the disease is varied. Observers in goitrous districts are impressed with a tendency toward a type of course in which there is a progressive intensification for several months of all the manifestations until a highly toxic and critical peak is reached. This crisis, if no treatment but rest is given and if the

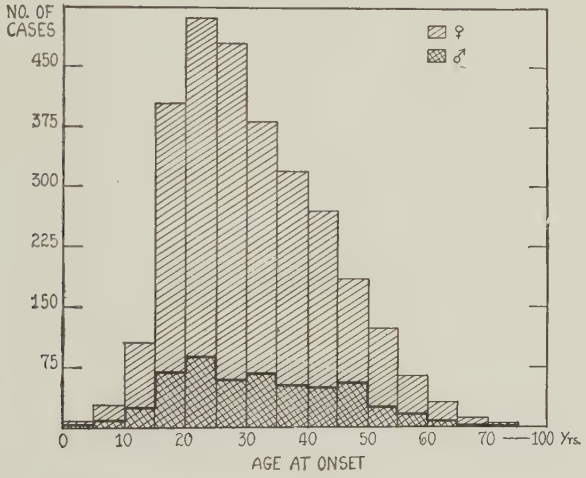

FIGURE 9. *Exophthalmic Goitre.* Age distribution curve, 3477 cases collected from the literature by Sattler.

patient survives it, in the course of a few weeks gives way to a period of sustained hyperthyroidism lasting perhaps several months more, and gradually subsiding during the next two or three years. Recrudescences may take place during this time at intervals of six months more or less. It is partly on the basis of a course such as this that Plummer[4] has erected his two-product theory of exophthalmic goitre, which we shall discuss later.

Our experience in Boston has been that, although a course

of the type just described not infrequently is seen, there also are a great many cases in which it is quite different. We are especially impressed with a more chronic type (see Case No. 68, chapter VI) where no definite toxic peak or crisis status is reached, but in which instead there is a thyrotoxicosis which remains of more or less constant severity indefinitely, perhaps for many years[26].

In the past much has been written about formes frustes, larval, and abortive types. This was for the most part before modern diagnostic methods were available. It is quite true that a variety of types of clinical course is observed, some acute, some chronic, some severe, some mild, some with relapses, some without, also some in which one or more of the customary manifestations is in intensity out of proportion to the others, as in many other diseases; but this does not, it seems to us, necessitate special terms for the less usual pictures.

We have been rather impressed in our own clinic with the scarcity of mild types in men. The male sex, although afflicted by this disease only about one-sixth as often as the female, seems prone to have it in a fairly severe form. The frequent mild types seen in women are in our experience rare in men. It has also seemed to us that in men the subjective symptoms are minimized, while in women the reverse often holds. Men usually are found to be more severely thyrotoxic than their symptoms would indicate; women, not infrequently, less so.

In children the classic picture is occasionally seen[27, 28]. Patients as young as one year of age have been observed[29]. We have had two boys (the history of one of which follows, Case No. 2265), one of seven and one of six and a half years of age.

Most striking is the mildness of the disease in childhood.

This mildness is only subjective, for while there may be striking exophthalmos, considerably enlarged gland, restlessness and tremor, the child will not admit that he feels ill and will want to play with other children and carry on as usual. The course of the disease in children, as recently observed in our clinic by Hertz, shows a great tendency to persistence and recurrence after rather radical subtotal thyroidectomy. On the other hand, in childhood early in the disease there may be marked chronicity with bouts of hyper- and hypo-metabolism of very striking character.

Etiology

Some of the earlier ideas on the causation of exophthalmic goitre were reviewed in the first chapter; the neurogenic theories of the French school, the thyrogenic theory of Moebius and the combined neuro- and thyro-genic hypothesis of Müller. Both Moebius and Müller thought that only certain persons, namely those with some sort of neuropathic tendency, could acquire the disease. This idea in one form or another has pervaded the literature since and has much to recommend it, though as yet it lacks proof.

Exophthalmic goitre has occurred in other animal species than man (Sattler), and Cannon's experimental work remotely approaches a successful artificial production of it in the cat. The predilection of the disease for females is quite like that of the other types of thyroid disorder and raises the question of a pituitary or ovarian background.

If we attempt to think of all the factors which might play either primary or secondary rôles in the causation of Graves' disease, the list would now be as follows; 1) hereditary, 2) constitutional, 3) racial, 4) geographic, 5) infectious, 6) extra-

thyroid endocrinous (including pituitary), 7) traumatic, physical and psychic and 8) nutritional.

From their nature it would be unlikely that the first three could be more than predisposing factors; they might load the gun, but another would be necessary to pull the trigger. Traumata, either psychic or physical, might be such trigger pullers, and occasionally they seem to be, but in the majority of cases they are lacking. Exposure of animals to cold for prolonged periods has, in our experience (Hertz) and in that of other workers, given histologic evidence of thyroid stimulation.

Infection perhaps by several or by some single specific virus is possible; McCarrison[30] favors this view, but very few share it for a variety of reasons which we hope will become apparent later. If Graves' disease turns out to be a deficiency disease, it is possible that infection in an extraordinary sense may play a rôle in as far as it may contribute to the latter by depletion of the body of some important substance which is required for normal thyroid function. We do know that infections, such as acute tonsillitis and pharyngitis, have a tendency to aggravate Graves' disease when it is already developed.

The relation to various other endocrine glands is veiled in obscurity despite recent advances which are constantly being made in this field. That sometimes the disease develops at the sex crises in women is admitted, but as it more often develops at other times, this does not clarify the situation very much. In the above series in only thirty-one of one hundred and twenty women was there definite association between onset of exophthalmic goitre and puberty, pregnancy, puerperium, or menopause.

We have seen typical exophthalmic goitre cases in which the precipitating factor seemed to be pronounced weight loss. In several instances the latter was due to voluntary dietary restrictions in psychotic individuals, to prescribed obesity diets with and without thyroid feeding and to loss of weight incidental to independent diseases, such as ulcerative colitis and peptic ulcer, which have preceded the development of the syndrome. Since the usual response to starvation is a lowering of the metabolic rate (Benedict[55]), we have interpreted these cases as examples of disturbed homeostasis. The possibility of a specific vitamin or food deficiency of course suggests itself in such patients as playing an etiologic rôle. That they occurred in the vicinity of Boston would militate against their being on an iodine deficient basis[56].

In recent literature the relationship of the pituitary gland (anterior lobe) to thyroid function has been stressed, and the hypothesis that exophthalmic goitre has a primary pituitary basis has seemed attractive to many authors. While a fair reproduction of exophthalmos, hypermetabolism and the characteristic partition of iodine between thyroid gland and blood stream as it exists in human exophthalmic goitre has been accomplished by injection of thyrotropic fractions of anterior pituitary in ducks, (Schackaert[57]) guinea pigs, (Friedgood[58]) etc., certain of the features of exophthalmic goitre are not so produced. The enlargement of the thymus and lymphatic system and the tendency to thyrotoxic crises leading to death have not been reproduced in animals by this means. On the other hand, the tendency to remission of the disease has been simulated in experimentally induced hyperthyroidism, and the inhibitory effect of iodide administration on such hyperthyroidism has been stressed. A human example of this mechanism

is given in Case No. 7793,a patient with acromegaly and anterior pituitary hyperthyroidism which responded to iodides.

Attempts to obtain evidence in the human in support of the pituitary hypothesis of exophthalmic goitre have been unsuccessful. Utilizing the hypophysectomized rat as test object, Hertz and Oastler[59] tested for thyrotropic hormone in the blood and urine of cases of exophthalmic goitre with negative results. The same method, applied to the body fluids of patients with myxœdema, yielded positive reactions. It would seem, therefore, on the basis of this study that there is little reason to maintain that the pituitary is hyperfunctionating in the ordinary case of exophthalmic goitre. This confirms the negative histologic studies of the anterior pituitary glands in such cases at post-mortem which is mentioned under Pathology.

That, rarely, the anterior pituitary does overact to produce stimulation of the thyroid in the human is attested to by the cases of acromegaly which show variable degrees of thyrotoxicosis in the early stages of the former disease. Hertz and Oastler contend that this is something apart from exophthalmic goitre and prefer to restrict the term "anterior pituitary hyperthyroidism" to these rare instances of such a relationship.

Of the possible contributing factors listed we believe that investigations of the first, fourth and eighth are most likely to bear fruit. While families are found occasionally in which several members are afflicted with Graves' disease, the matter of inherited inferiorities and susceptibilities is the factor of chief importance. Of geographic factors all that can be said is that the disease is found in both goitrous and non-goitrous regions. There is no accurate way of getting at its incidence. It is not a reportable disease, and death reports are

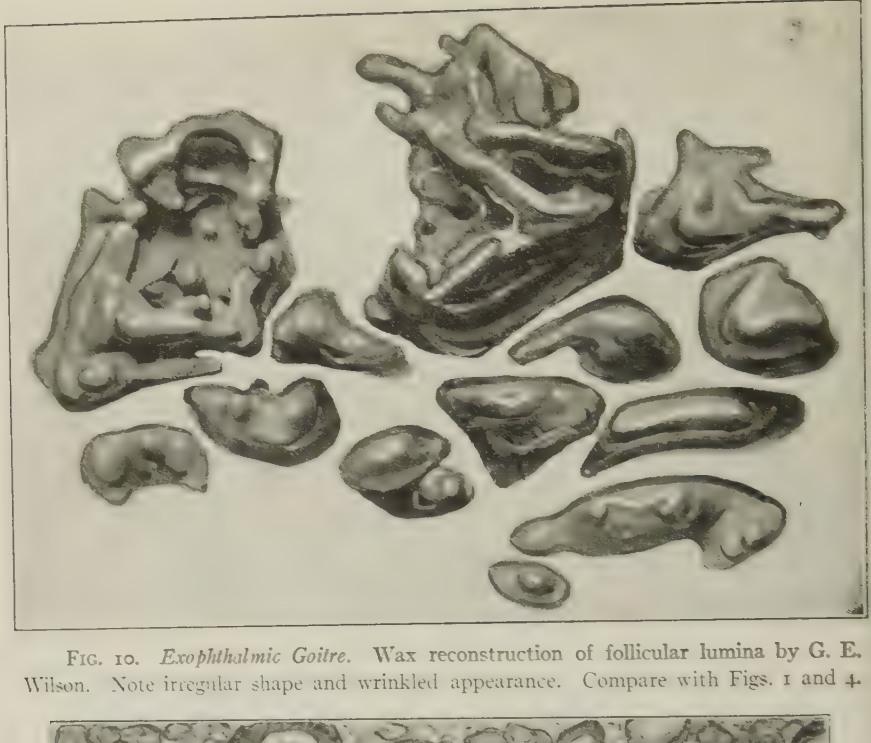

FIG. 10. *Exophthalmic Goitre.* Wax reconstruction of follicular lumina by G. E. Wilson. Note irregular shape and wrinkled appearance. Compare with Figs. 1 and 4.

FIG. 11. *Exophthalmic Goitre.* Low power camera lucida drawing, showing type of hyperplasia frequently seen in patients who have received no iodine. Note marked infolding of epithelium, scarcity of colloid, increased vascularity, and lymphoid infiltration.

of little value, because nowadays only a small percentage of patients afflicted with exophthalmic goitre die of that malady.

From the psychiatric point of view our clinical material gives isolated evidences of some tie-up between the affective life of the individual antecedent to the development of thyrotoxicosis and a possible sympathico-adrenal disturbance through a pathologic condition in the hypothalamic centers concerned in emotional life. This seems to us to be a more modern modification of the thoughts of Moebius and Müller and drives us back to the idea that it often seems likely that persons who acquire exophthalmic goitre are predisposed to the syndrome by some inherited or acquired inferiority, and whether we call this autonomic imbalance[31] or something else matters very little, for the name we give it throws no light on its nature.

Pathology

The morbid anatomy of exophthalmic goitre, as far as the thyroid is concerned, can be summarized in the words parenchymatous or follicular hyperplasia. Grossly, the outstanding features are the diffuse enlargement and the marked vascular engorgement. When removed from the body and drained of blood, the gland feels firm and appears finely and coarsely lobulated; on section it looks pink and gray.

Histologically the important features are those noted by Müller[3], namely, increase in the height of the epithelium and in the number of epithelial cells, which brings about wrinkling or puckering in the follicular wall and presents on section the appearance of papillary ingrowth. There is usually also a diminution in the amount of colloid, often lymphoid infiltration in the interstitial tissue, and in the long-standing cases increase

in the connective tissue. By special staining methods, as Goetsch[32] pointed out, increase in the mitochondria of the parenchymal cells can be demonstrated. The puckering brought about by the increase in cells and decrease in colloid of the follicles is very beautifully illustrated in the wax model constructed by Wilson[33] from one of our cases (Fig. 10). The impression this makes as compared with the smooth normal follicle shown in Fig. 1 is of a shrivelled up affair, although the actual process, of course, as far as the wall is concerned, is the opposite of shrivelling; it is rather a redundancy.

The amount of colloid can be increased definitely by giving iodine[34]. Comparison of the glands removed before pre-operative saturation with iodine was practiced, with those removed since, shows these changes very strikingly. Typical examples of the former and the latter are shown in Figs. 11, 12, and 13.

Outside of the thyroid there are some important features. The increase in postorbital fat and engorgement of the vessels behind the eyeball have been mentioned. Of other organs showing characteristic changes the thymus heads the list. We have recently analyzed twelve autopsies (eleven female, one male) on patients with exophthalmic goitre, these being all that occurred among five thousand autopsies over a thirty year period at the Massachusetts General Hospital. Five of the patients died following operation; the other seven were not operated on.

In nine of the twelve the thymus was persistent, weighing from 4 to 90 gm., and in four of these nine there was in addition the full picture of status thymico-lymphaticus with enlarged spleen and lymph nodes. The significance of these findings is not clear, but they are quite like those of other observers.

The hearts, except in a few instances, showed surprisingly

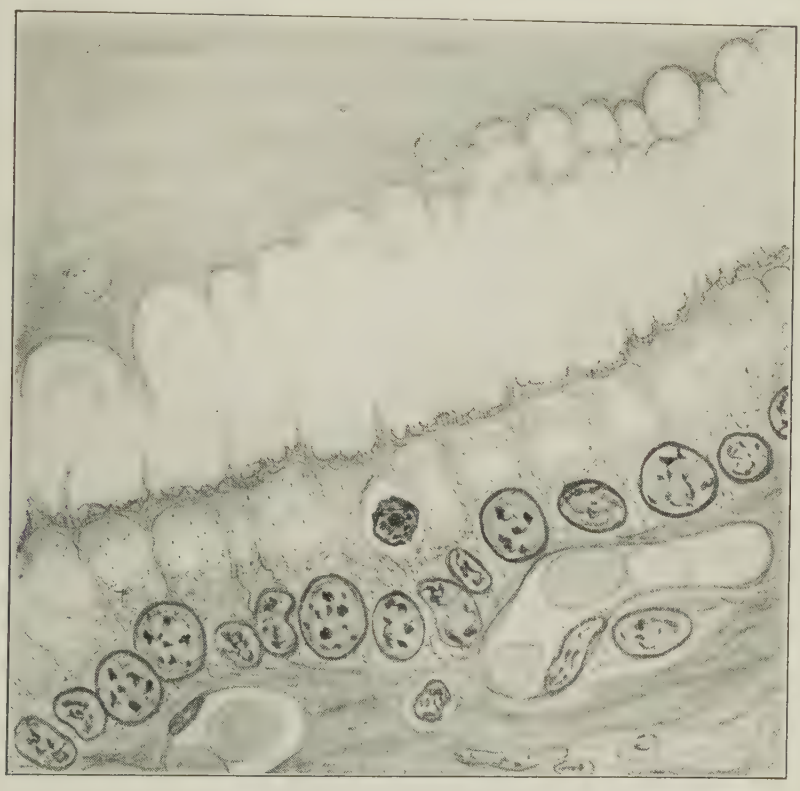

FIGURE 12. *Exophthalmic Goitre.* High power camera lucida drawing. Note the high columnar epithelium. Compare with Fig. 3.

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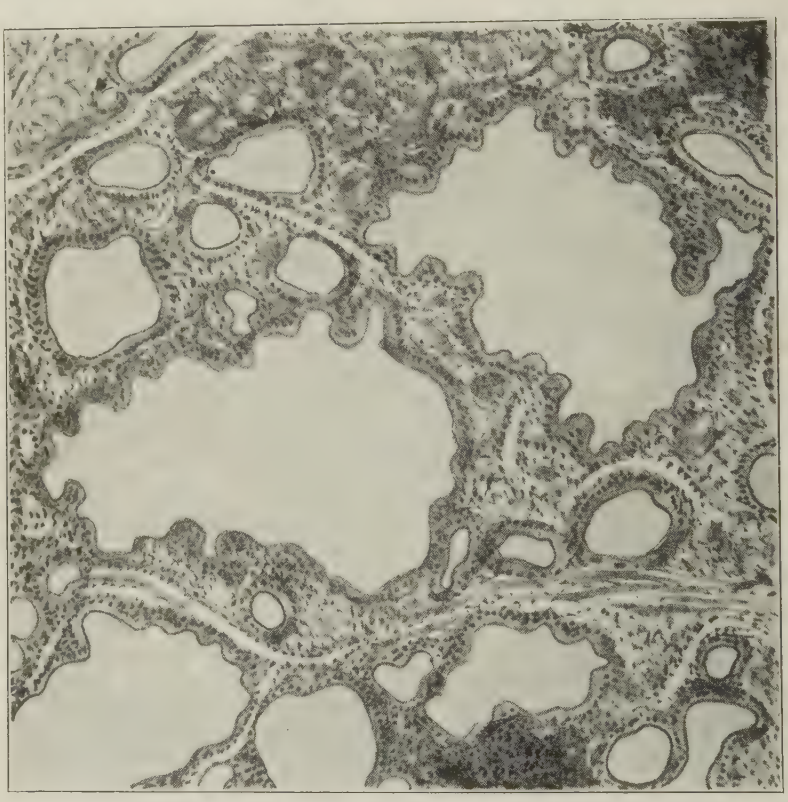

FIGURE 13. *Exophthalmic Goitre.* Low power camera lucida drawing, showing the appearance often seen in persons who have received iodine. The amount of colloid is increased but the papillary infoldings remain.

Facing page 139.

little hypertrophy. The average weight in ten of the female subjects was 287 gm. with a maximum of 365 gm., and in the eleventh it was described as rather small but was not weighed. The weight of the heart of the one male subject was 375 gm. The adrenals, pancreases, livers, kidneys and ovaries showed no significant changes, and there was no evidence of premature arteriosclerosis. In brief, therefore, the morbid anatomy outside of the thyroid may be summed up as a highly characteristic and frequent persistence of the thymus[35, 36] and not infrequent complete status thymico-lymphaticus (present in a third of the series), together with occasional slight hypertrophy of the heart.

Lesions in the liver have been described, and Sanger and Hun[37] have expressed the belief that there is decreased ability to store glucose, due to liver damage. Richardson, Levine, and DuBois[38], however, obtained results contradictory to this theory.

Recent autopsies on exophthalmic goitre patients have revealed no gross abnormalities of the anterior pituitary, and histologic examination of these glands has given no evidence to support the view that the disease is associated with anterior pituitary over-activity. In two instances the anterior pituitary glands seemed somewhat smaller than normal but did not show significant decreases in any of the individual cell types or any regular cytologic abnormalities which could be recognized by ordinary staining methods (Hertz).

Theories of Causation

Since in the majority of cases of exophthalmic goitre no etiologic agent or likely causative factor thus far has been found, and since the disease has not been perfectly reproduced experimentally, it must be admitted freely, that in contrast to endemic goitre, the cause of the disease remains quite unknown.

Speculation, however, is permissible, and it is even desirable that the practitioner be familiar with some of the better known theories, and particularly desirable that he realize that they are but theories, for otherwise he may become quite bewildered by the various diametrically opposed views held by leading authorities.

Marine[39], for example, recently has stated his view; "that underlying the typical clinical picture of Graves' disease there is a long standing constitutional anomaly which may be acquired or inherited (congenital), the acquired form coming on usually in association with or after the menopause, the thyroid hyperactivity being secondary and a result of a powerful stimulation either through the sympathetic nervous system or through the blood stream or both. To determine the origin of this stimulation of the thyroid, as well as that of other tissues, particularly the lymphoid (thymus and lymph glands) is the major problem in connection with this disease."

The powerful and unaccustomed stimulus concept is also the central idea of H. S. Plummer's[4] hypothesis, although in other respects his views and Marine's are widely divergent. This disagreement is very likely because the latter has focussed his attention chiefly on the histologic picture and the iodine content of the thyroid gland, whereas the former has focussed his on the symptoms of the disease. Marine believes that the essential physiologic disturbance is an insufficiency, and the hyperplasia compensatory; Plummer believes that the gland is fundamentally hyperfunctioning, but usually in a pathologic way.

The word hyperthyroidism, introduced first by C. H. Mayo[40], although the idea had been expressed by Moebius[41] sixteen years before, has perhaps been the chief storm center in the contro-

versy on the nature of Graves' disease. On the one hand we may find writers such as Lahey[42] who use the term "primary hyperthyroidism", in our opinion a misleading one for it suggests that the thyroid is primarily at fault, as synonymous with exophthalmic goitre, and others such as Hoover[43], who says: "There certainly is no evidence for superfunction of the thyroid gland as a cause for Graves' disease. All the evidence seems to indicate that hyperplasia so-called is evidence of incompetence of the gland and is associated with hypofunction instead of hyperfunction."

Many other conflicting opinions could be cited, but for our present purpose a critical examination of the theories of H. S. Plummer is most likely to be helpful. These in brief, as we interpret them both from his published writings and from conversation, are somewhat as follows. In the first place he was struck by a marked lack of relationship between the intensity of what he took to be hyperthyroidism, as judged by basal metabolism, and the intensity of the symptoms, ocular and nervous, characteristic of Graves' disease; the latter might be well marked when the metabolism was low or absent, or slight when the metabolism was high. This lack of correlation suggested that two morbid agents were at work; the first, responsible for the metabolism elevation, he assumed to be an excess of normal thyroxin; the second he thought might be an abnormal thyroid product of some sort. In other words, in Graves' disease we have a gland which hyperfunctions and thereby increases the concentration of thyroxin in the tissues, thus elevating the rate of metabolism and giving the symptoms which we can produce by feeding thyroid tablets to normal persons; and in addition it forms an abnormal toxic product which produces the eye signs, and nervous and mental symptoms which become marked, par-

ticularly during crises. This is Plummer's two-product theory, and he goes further with it to the point of suggesting that the abnormal product is in reality an incompletely iodinized thyroxin, though on this last he does not insist. This conclusion, based largely on the effect of iodine, we shall scrutinize presently.

The sequence of events, Plummer fancies, may be that first an intense stimulus or drive attacks the thyroid; the nature of this stimulus he admits is quite unknown. The stimulated thyroid responds by hyperfunction and hyperplasia. If the drive comes on very suddenly in, as he calls it, an "untrained" gland, particularly if the iodine supply is low, there is made chiefly a faulty and toxic type of thyroxin, faulty because its molecule possesses too little iodine. This substance produces the eye signs, the hyperirritability, the emotional instability, and intoxication which in many ways is comparable to acute and chronic alcoholism.

If the stimulus continues, the gland by degrees becomes "trained" to it and makes more and more normal and less and less abnormal thyroxin; in brief, a dysthyroidism gradually becomes converted into a simple hyperthyroidism. If large doses of iodine are given, this conversion is greatly accelerated. A theory of this sort, providing as it does at least three independent variables, namely, the intensity and duration of the stimulus, the availability of iodine and the functional capacity of the thyroid, is capable of explaining a wide variety of clinical pictures and modes of progression of the disease. Whether it is the correct explanation is another matter.

It would be beyond the scope of the present work to enter upon a long critique of these conflicting views. It is evident that no one knows the primary cause, and that there

are those who believe the thyroid is guilty of any one of the following, or of both of the last two; hypofunction, dysfunction, hyperfunction.

Our own view is that there is overwhelming evidence in favor of thyroid overactivity of some sort. We know, for example, that the administration of thyroid substance constantly elevates metabolism in normal subjects and in them produces some of the symptoms found in Graves' disease. We also know that in Graves' disease the metabolism is invariably elevated. We know that subtotal thyroidectomy removes in large measure the symptoms of the disease. We further have an imposing array of opposites, clinical, physiologic and biochemical, between known hypothyroid states and Graves' disease. While all this may not constitute complete proof of hyperfunction, it at least throws the burden of proof upon him who claims hypofunction. If hypofunction is assumed, some adequate non-thyroid cause of the increased metabolism must be found, and personally we believe that impossible.

In regard to Plummer's theory we are on less certain ground. For several reasons we are unwilling to accept it without reservations. Nevertheless it provides in the main a seemingly reasonable explanation for more of the peculiarities of Graves' disease than does any other theory so far devised.

The outstanding advance in our knowledge of Graves' disease, which Plummer has made, is the discovery of the characteristic reaction to iodine. Of course iodine had been used by many before Plummer. Kocher[44] had used it and condemned it. Marine and Lenhart[45] had advocated it in small doses, but to Plummer belongs full credit for the demonstration that after large doses there occurs a remarkable and sudden decline in symptoms and a characteristic fall in metabolic rate. To combat

any claim of priority over Plummer it can be pointed out that iodine is now used throughout the United States in the treatment of exophthalmic goitre differently both in purpose and in manner from any practice that existed before his work was

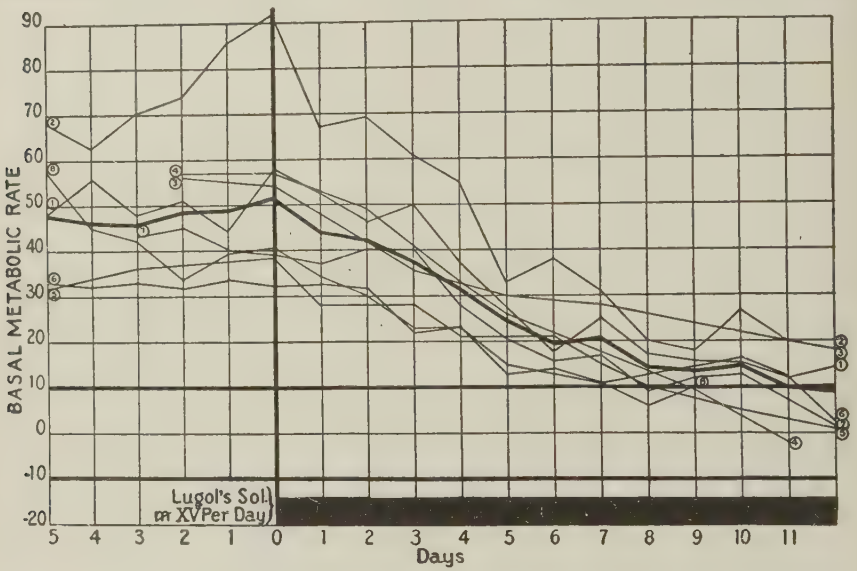

FIGURE 14. *Effect of Iodine in Exophthalmic Goitre.* Basal metabolism curves in eight cases receiving Lugol's solution. The heavy line is the composite. (After Starr, Segall, and Means.)

done. He at least deserves the credit for having told the world about the iodine phenomenon in exophthalmic goitre.

THE IODINE REACTION

Immediately upon the announcement of Plummer's discovery, the effect of iodine in the form of Lugol's solution was studied in a series of cases in our clinic[46]. The results on metabolism are shown in Fig. 14. In each of eight patients observed daily under ideal circumstances there was a progressive fall in metabolism until on from the fifth to the tenth day a normal level was reached. The average rate of fall in basal metabolic

rate was 3.7 points per day, which interestingly enough is precisely the same as that found the year before in a similar series, similarly observed, after subtotal thyroidectomy without iodine[48]. Entirely parallel drops were obtained in pulse rate. Since the first study a larger series of cases has been obtained

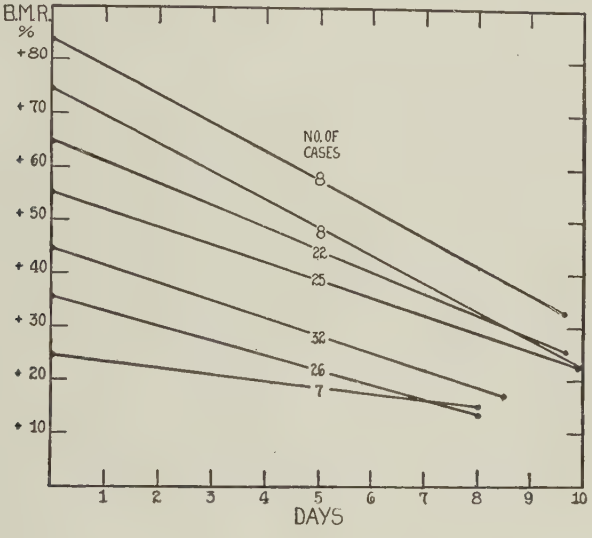

FIGURE 15. *Effect of Iodine in Exophthalmic Goitre.* Metabolic rates in 128 cases before and after the iodine response. The cases were grouped in accordance with the pre-iodine levels, each 10 point interval constituting a group.

in which iodine in the form of Lugol's solution has been given according to Plummer's methods. The results obtained in these are shown in Fig. 15. Daily basal metabolism determinations were not made, but the level before Lugol's solution was given has been compared with the lowest point obtained after it and the length of time required for the drop. The data are therefore less exact in the individual cases than those of the first series, for in some instances only one pre-Lugol determination was made. Against this can be set the fact that the series is much larger, and since the results in general are in agreement,

we consider it reasonable to draw certain definite conclusions from the average curves.

The series has been analyzed in Fig. 15 by the method of separation into groups according to the pre-Lugol rate. The average basal metabolic rate before and after the drop for each group is then plotted against the average time required for the drop. It has been shown that Lugol's solution in the dosage recommended by Plummer has no effect on the basal metabolism of normal persons[48, 49], and it is interesting therefore to note that the curves shown in Fig. 15 tend to become flatter and flatter as their starting points approach normal, which suggests in this respect a balanced chemical reaction. The rate of fall of the highest curve, for example, is 5.7 points per day, that of the third, 4.1 per day, that of the fifth (which most nearly corresponds with the Starr, Segall and Means group, where the rate of fall was 3.7), 3.2 per day, and that of the seventh 1.5 per day. The magnitude of the iodine drop taken as a function of the frequency is as follows:

	No. of cases
No drop	6
5–20 points drop	20
21–30 " "	36
31–40 " "	31
41–50 " "	25
51–60 " "	9
61–70 " "	2
71–80 " "	1

or as a percentage of the original level:*

	No. of cases
No drop	6
1–10 % drop	0
11–20 % "	4

* Two cases added, not included in Fig. 15.

	No. of cases
21–30 % drop	3
31–40 % "	6
41–50 % "	16
51–60 % "	23
61–70 % "	29
71–80 % "	25
81–90 % "	10
91–100 % "	8

In other words 71 per cent. of the cases showed drops of between 21 and 50 points, and of between 41 and 80 per cent. of the pre-iodine level. Before the use of iodine, drops of this rapidity and magnitude in exophthalmic goitre, except as isolated occurrences, took place in our clinic only after subtotal thyroidectomy. The basal pulse rates have not been similarly analyzed in the larger series for the reason that there is no doubt that the metabolism is a more exact guide to degree of hyperthyroidism. Correlation between pulse and metabolism in general has been discussed in Chapter II, and it may be said here, in view of the experience in individual cases, that the parallelism between these factors during the Lugol drop is striking, sufficiently so that were metabolism tests not available, the pulse would provide a less exact but still fairly satisfactory means of quantitating the drug action.

It seems to us safe to conclude that the metabolic phase of the iodine reaction in exophthalmic goitre, as we see it in Boston, Mass., a non-goitrous region, is a fairly certain and predictable affair. We say, "as we see it in Boston", for it cannot be emphasized too strongly that geographic factors may alter the nature, course and reaction of the disease.

The metabolic phase, however, is by no means the whole of the iodine reaction. Plummer's claims of the effect of Lugol's solution on the nervous and mental characteristics of exophthal-

mic goitre have been confirmed abundantly in the Massachusetts General Hospital clinic. It has been our practice to ask patients how they feel after they have had iodine for a few days. Almost without exception they will state enthusiastically that they are greatly improved, and when asked to analyze this, they reply that they are no longer irritable, restless, frightened, anxious, or depressed, and that their heart does not pound so hard. This information they will volunteer, no leading questions whatever having been asked. Nor is the improvement subjective only. The appearance changes markedly. The continuous motion ceases, the frightened expression goes, the pulse and heart action become quiet, and the tremor decreases or disappears. In some cases the bruit over the thyroid decreases or stops entirely after the iodine remission has occurred. An extreme instability of the vasomotor system giving rise to flushings, particularly about the elbows, as Plummer has pointed out, we have seen abolished.

These symptomatic happenings, in terms of Plummer's theory, are due to a cessation of the manufacture of an abnormal type of thyroxin. To explain the drop in metabolism he is forced to the assumption that the abnormal, like the normal form of thyroxin, has a calorigenic action. When, after an iodine remission, the metabolism slowly climbs back to its previous high level in spite of the continued administration of the drug, as for example in the cases shown in Fig. 16, Plummer would say that the phenomenon is due to a gradually increasing simple hyperthyroidism, not to a return of the peculiar exophthalmic crisis status. The pathologic stimulus is still activating the gland, but in the presence of an adequate supply of iodine only an excess of normal thyroxin results. Plummer goes so far as to say that what we term a crisis in exophthalmic

goitre is a status dependent solely on the abnormal or bad product, and it can never occur so long as iodine saturation is maintained, even though metabolism may go to very high levels. Our experience at the Massachusetts General Hospital has been in part, but not completely, consistent with this interpretation.

It is by no means an unattractive hypothesis, that the suddenly stimulated thyroid can never respond except by the

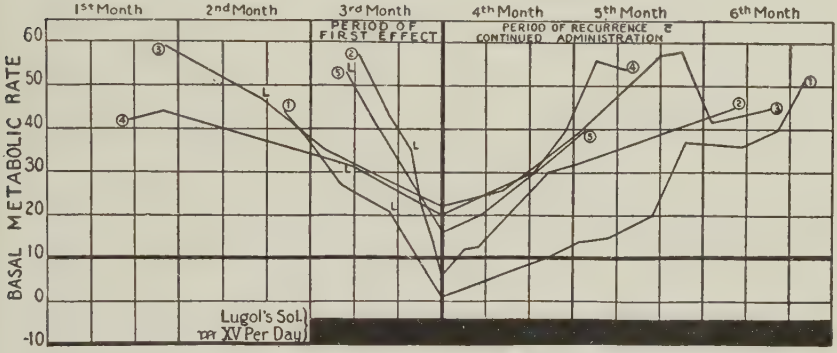

FIGURE 16. *Exophthalmic Goitre.* Return to a high level of metabolism during continued administration of iodine. "L" denotes the point at which iodine was begun in the individual cases. (After Starr, Segall, and Means.)

production of faulty thyroxin. But however it works, we are bound to infer, if the two-product theory is true at all, that in Graves' disease under the influence of iodine the faulty product disappears from the blood and hence from the tissues, either because the thyroid no longer makes it, or because it is locked within the gland and not permitted to escape. Either of these happenings might explain both the disappearance of the phenomena of Graves' disease and the fall in metabolic rate which takes place.

The development of quantitative methods for the determination of small amounts of iodine have added to our knowl-

edge that the thyroid gland contains large quantities of iodine. By the von Fellenberg method of micro-determination it is now possible to detect 0.0001 mgm. of the element in such biological materials as urine and blood.

The normal thyroid gland contains about 10 mgm. and approximately 40 mgm. per 100 grams of fresh tissue. There is considerable variation in iodine content of glands in different geographical regions. In certain localities iodine content of thyroid glands may drop to 8 mgm. in the winter months. Patients with exophthalmic goitre have as low as 3 mgm. total iodine content of the gland.

Normal blood iodine value is about 12 micrograms per 100 c.c.[60] In toxic goitre patients it may rise as high as an average of 27 micrograms (11 patients investigated by Curtis et al.). However, Curtis found no correlation between degree of hyperiodemia and basal metabolic rate. Patients with untreated myxœdema have a lowered blood iodine, as low as 4 micrograms per cent., which is the value for inorganic iodine in human blood when fractionated into alcohol-soluble and insoluble portions, the latter being the "organic or thyroxin iodine" (8 micrograms) per cent.

Studies of Curtis and Phillips[60] have further indicated that, whereas there is considerable variation of urinary excretion of iodine on ordinary diets, in normal individuals on a relatively standardized dietary regime the average daily excretion is about 55 micrograms. Many careful balance studies have not as yet been reported, but on one normal male subject under strict hospital control 156 micrograms were injected, and the daily excretion was 43 to 53 micrograms, an average of 48 micrograms. A slightly lesser daily excretion occurred in a normal female after the injection of 56 micrograms daily,

namely, an average of 35 micrograms. These authors indicate that there is a considerable daily loss of iodine in the stool and sweat. They report that in eleven patients with thyrotoxicosis there was a daily iodine loss in the urine of 65 to 310 micrograms, an average of 157 micrograms. The blood iodine values in this series of patients ranged from 14 to 35 micrograms, and averaged 26 micrograms per cent. and basal metabolic rates ranged from plus 18 to plus 109; therefore Curtis et al. believe that in thyrotoxicosis there is a true "iodine diabetes" as an essential aspect of the disease.

Perkin[61] working in Boston found normal blood iodine values to range from 1.1 to 18.3 micrograms per cent. and established 10 micrograms as the upper limit of normal. Non-toxic goitre patients had values from 2.0 to 12.8 micrograms per cent. The average values for both groups were 6.6 micrograms per cent., whereas in a group of 174 cases of "primary hyperthyroidism" the average value was 21.0 micrograms per cent., and the range was from 2.0 to 149 micrograms per cent. Thirty per cent. of this series exhibited normal blood iodine values irrespective of the degree of toxicity obvious clinically.

Perkin[61] has described an iodine tolerance test carried out in a manner analogous to the ordinary sugar tolerance test and describes a flat curve after the administration of a standard amount of Lugol's solution (37.5 mg. I_2) in thyrotoxic patients as compared with the steep curve which occurs in normal and non-toxic goitre patients. Theoretically, the hyperplastic gland, which is deficient in iodine, withdraws the administered iodine more rapidly from the circulation than does the normal or non-toxic gland. It is obvious, however, that there may be other explanations for the rapid disappearance of the iodine from the circulation in toxic goitre patients, namely excretion in increased

amounts in the urine. Careful balance studies in this field are needed.

Some of the difficulties that we find in accepting Plummer's theory in toto are these. First, were cessation of manufacture of a faulty product due to better iodinization of the thyroxin molecule, we should expect a simple hyperthyroidism to develop immediately following the disappearance of the dysthyroidism, with but little change in metabolic rate, but such is not the case. Still more difficult to reconcile with Plummer's theory is the effect of iodine late in the disease. Over and over again we have found that both basal metabolism and the peculiar Graves' symptoms respond quite as well after years of chronic exophthalmic goitre, as early in the disease, when, as Plummer puts it, an "untrained" gland may be acted upon by an intense and unusual stimulus. The glands of these long-standing cases should have had ample time to become "trained" to the hypothetical stimulus, and to produce normal thyroxin, but actually they appear not to have.

Perhaps the most satisfying form of the two-product hypothesis is to look upon the thyrotoxicosis of exophthalmic goitre as made up of two components, one of which can be held in abeyance so long as an excess of iodine is present; this we may call A, the other of which, uninfluenced by iodine, we may call B. The actual thyrotoxicosis of any given patient at any given time will be represented by the sum A plus B, or, if an excess of iodine is being taken, by B alone, A having been eliminated by the excess of iodine. Such terminology is perhaps more consistent with our present meagre knowledge than the use of such labels as "good" or "bad" products of whose existence we have no direct proof.

Another important concept is that the progress of the dis-

ease is uninfluenced by taking iodine, although the character and intensity of the thyrotoxicosis at any given time can be altered by so doing. Iodine in no sense cures the disease or retards its course; it merely modifies certain of its features making them less malignant than they would be without its beneficial influence.

The ratio of the components A : B will vary from patient to patient, from place to place and in the same patient from time to time. As the disease runs its course, important changes in the ratio undoubtedly occur, and the relative magnitude of the influence to be had by saturating the patient with iodine will vary accordingly. There is reason to believe that in many cases we have A greater than B early and late in the disease, with an intermediate phase in which we have A less than B.

The natural course of the disease unquestionably is very varied. If we plot components A and B as curves, they will trace a variety of shapes, sometimes a sharp peak, sometimes a long plateau, sometimes a chain of hills. The course varies from that of the very acute case ascending rapidly to a dangerous toxic crisis, to the very chronic one with essentially the same status year after year. Heredity, constitution and locality, as well as countless other factors, may play a part in determining the shape of the course.

It is altogether likely, as Plummer has claimed, that the chief dangers of the thyrotoxicosis, sudden death, extreme nervous and mental excitation are bound up with A rather than with B.

Beyond this, with the facts we now have, the problem, though fascinating, is, we believe, insoluble. The important thing for the practitioner is to separate fact from fancy. We can list as facts that large doses of iodine bring about 1) a characteristic remission in exophthalmic goitre, consisting in a

rapid amelioration or removal of the characteristic phenomena of Graves' disease, 2) an abrupt drop in metabolism and pulse rates reaching or approaching normal levels in ten days or less. This remission is sufficiently constant to be diagnostic, and it may occur in any stage of the disease, early or late. The nature of the reaction and the mode of action of the iodine remain obscure. The added facts, however, that iodine does not alter energy metabolism when given to normal persons and that it has no action in reducing metabolism or altering symptoms in hyperthyroidism induced by feeding thyroid gland are pertinent.

We believe that for the present at least it will be wholesome for the profession to look upon the action of minute amounts of iodine in preventing endemic goitre as being in its nature very different from that of far larger quantities in bringing about detoxification in exophthalmic goitre. Discussing some of the paradoxes of the effects of iodine upon the thyroid, Leo Loeb[50] ventures the belief that ordinarily the gland is under hormone control. Lack of iodine under these circumstances acts as a stimulus. The thyroid of Graves' disease, he believes, is out of hormone control, and the mechanism whereby iodine diminishes its activity is quite obscure. The original stimulus to the gland in exophthalmic goitre presumably is not iodine lack as in the case of endemic goitre.

Illustrative Cases

Case No. 3994. *Exophthalmic Goitre, Acute Type, with Abrupt Onset without Known Cause*

History. — A Cape Cod Portuguese farmer, 47 years old, father of five healthy children, of good habits and with unimportant past history, entered the hospital May 22, 1926, complaining of pain in the region of the heart and swelling in the neck of four months' duration. Previous to that he had been, so he believed, in perfect and vigorous health, weighing 98 kgs. His illness began with an attack of vomiting coming on without known cause and lasting a day, and being replaced by extreme nervousness and shaking. Two days later his doctor was sent for and found him with a coarse tremor of the entire body, so marked that he even walked with gross unsteadiness. The slightest noise would make him jump. The day following he developed a pain in the region of the heart, sometimes sharp, sometimes dull, which persisted along with the nervousness to time of entry.

Apparently no treatment had been given, and the patient states he was told that he was going insane. After the symptoms had persisted for two and a half months, he noted that his neck was beginning to swell. This varied from day to day, being greater at one time than another. His appetite, previously very good, had been poor ever since the onset of his ailment. There had been no diarrhœa and indeed no subjective symptoms except those already noted. There had been a loss of 23 kgs. during the four months.

Examination. — Physical examination showed a well built man who evidently had lost considerable weight. The eyes showed a wide fissure and slight exophthalmos but no other signs. Both lobes and the isthmus of the thyroid were moderately enlarged, the right somewhat more so than the left. The consistency was firm and slightly nodular. No murmur was heard over the thyroid. The tonsils were enlarged. The skin was warm and moist. The extremities showed a marked tremor. The remainder of the physical examination was not remarkable.

Management. — The patient remained in the hospital until June 19, 1926. The temperature was within normal limits throughout. The blood and urine were quite negative. The patient gave the impression of being remarkably stolid and non-introspective in spite of his evident toxic status. Iodine was given and a hemithyroidectomy done. The data were as follows:

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
May 22.				Blood pressure 160/80
" 25	+91	132	66.5	
" 27	+83	121	66.1	
" 28				Blood pressure 150/80.
" 29	+63	112	65.3	Lugol's sol. m. 45 (3 cc.) begun.
June 4	+74	108	62.1	Lugol's sol. m. 45 (3 cc.)
" 8				Blood pressure 130/65
" 9	+91	107	58.5	Lugol's sol. m. 45 (3 cc.).
" 10				Right hemithyroidectomy.
" 18	+65	98	53.8	Lugol's sol. m. 30 (2 cc.).
" 19				Discharged. Lugol's sol. m. 5 (0.3 cc.)
July 19	+50	114	62.3	

Comment. — This case has a number of instructive features. First, the very abrupt onset without known cause in a person previously in splendid health, together with steady progression, is representative of a certain type of Graves' disease. Second, the relatively subdued character of the subjective symptoms as compared with physical signs and general appearance of thyrotoxicosis. This we have found frequently in men who seem on the whole to have symptoms less intense than their actual intoxication would seem to warrant, whereas in women the reverse often holds.

The patient was exceptional in that although suffering from undoubted exophthalmic goitre, there was no bruit over the thyroid and he was one of the very few who failed to show the characteristic response to iodine. It was on this account that the operation was limited to hemithyroidectomy, and it is of interest that, as is frequently true, the operation was inadequate to abolish the thyrotoxicosis. When last seen, he was still thyrotoxic and further surgery was advised but not accepted.

Case No. 2077. *Exophthalmic Goitre, Chronic Type, with Insidious Onset*

History. — A State of Maine housewife of 24 years was admitted to the hospital July 13, 1923, with chief complaints of nervousness and asthenia from which she states she had suffered for at least ten years.

These had increased somewhat since her marriage five years before entry. She had had three miscarriages and then had given birth in rapid succession to three children, the youngest being one and one-half years old at time of entry. Other symptoms suggestive of Graves' disease were as follows: dyspnœa, palpitation, tachycardia, increased sweating, increased appetite, irregular catamenia, dislike of hot weather, and loss of weight. These apparently had been present and gradually increasing for about a year, though no definite date could be set for their commencement. In a year she had lost 12 kgs. and for three months had felt too weak to work. The eyes had been noted to be prominent for four months only, but her neck, she thought, had had a fullness all her life. There were no other facts in the past history which seemed to have a bearing on the present difficulty.

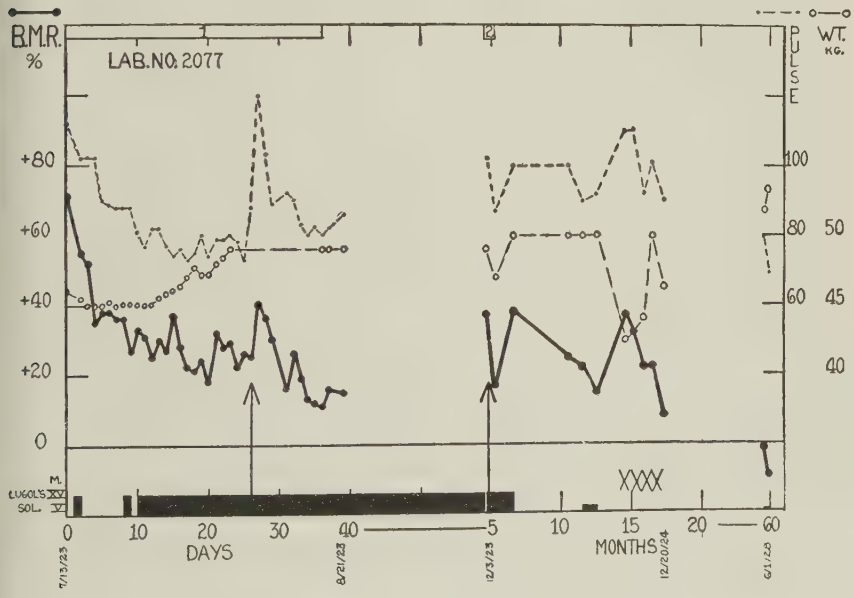

FIGURE 17. *Exophthalmic Goitre (Case No. 2077).* In this and all subsequent charts (except Fig. 19) periods in the hospital are shown thus [1] [2] at top; Iodine administration thus, [▪▪▪] at bottom of the chart; X-ray treatments thus, X; operation thus, ↑. For description in each case see text.

Examination. — This showed a restless and apprehensive woman with frightened appearance. The eyes were moderately prominent and lid lag was present. The skin showed some generalized increase in pigment and was hot and very sweaty. The thyroid was moderately and symmetrically

enlarged, with smooth surface and marked pulsation, thrill, and bruit. The heart was not enlarged but action was forceful, the sounds loud and ringing. A systolic murmur was present at the apex. There was marked tremor of the extremities. In other respects, the physical findings seemed unimportant. The blood pressure was 130/70 and the blood and urine negative.

Management. — Iodine was given with characteristic response, as shown in the chart (Fig. 17). Coincident with this the symptoms and signs declined materially and a hemithyroidectomy was done when the metabolic rate was steady at about plus 25 per cent.

Following operation, there was further fall in metabolism and the symptoms almost completely disappeared. She was discharged on August 16, 1923, taking Lugol's solution, m. xv (1 cc.) per day.

On November 30, 1923, however, in spite of continuation of this dose of Lugol's solution, she reported with a return of symptoms and signs, an enlargement of the remaining left lobe, and a basal metabolism of plus 37 per cent. A second thyroidectomy was done, again with improvement. Lugol's solution, m. xv (1 cc.) per day was continued for two months. She was nearly symptom-free for a time, but in May, 1924 had a definite relapse with return of the thyrotoxic symptoms. This time an improvement was brought about by X-ray therapy.

Comment. — In sharp contrast to case No. 3994, this one illustrates a very insidious onset. The precise beginning of the true Graves' manifestations could not be dated within years nor could the effect of pregnancy be identified. Nevertheless, there is no question about this case being one of true exophthalmic goitre. The beginning was simply gradual instead of abrupt. The disease furthermore proved more resistant to treatment than many of the more acute types.

Case No. 2831. *Exophthalmic Goitre with Acute Onset, Remission and Relapse*

History. — A forty-eight year old German-American widow with three children entered the hospital October 9, 1924, with the story that two years before, up until which time she had been in splendid health, she had noted bulging of her eyes and weakness. These appeared rather acutely and in the course of a fortnight she was so fatigued that she went to bed. She was also extremely nervous at this time, but in a few weeks more a distinct improvement occurred in all her symptoms which lasted for eighteen months, although six months after the onset an enlargement in the neck was first noted.

Six months before entry the symptoms all recurred: nervousness, asthenia, increase in exophthalmos, together with marked trembling of arms and legs and violent pounding of the heart. A sensation of warmth and dislike of warm weather began, and sweating became increased. There was also a marked polydipsia. A fine pigmentation had appeared on the back of the hands which she was sure was not there before the first onset. Furthermore, before the beginning of her illness she had for years been constipated, but since its onset she had had regular loose stools without catharsis. A change in personality had occurred in that before her illness she had been quite placid whereas since, she had been much irritated by little things. She also had talked much more and faster. Severe morning headaches had been present for three weeks only. Nine kgs. had been lost in three years. There had been no appetite increase.

A possible causative factor was found in the emotional strain incident to the death of a much loved husband three years previously, together with the sole responsibility for supporting her three children which obliged her to accept work in a box factory.

She had had malaria, appendicitis, and frequent colds in the past, but there was nothing in her past history that seemed to bear upon the present illness.

Examination. — This showed a thin, tremulous, middle-aged woman, highly emotional and frequently on the verge of tears. The eyes were moderately prominent and there was lid lag. The skin was warm and moist. The thyroid was diffusely enlarged with bruit over the left lobe. The heart was not enlarged but there was a systolic murmur at the base. There was a fine tremor of the fingers. The tonsils were large and cryptic. In other respects the physical examination was negative and the routine examination of blood and urine showed nothing of importance.

Management. — A diagnosis of recurrent exophthalmic goitre was made, and subtotal thyroidectomy was done in an iodine remission, with satisfactory relief, as the following data indicate:

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
Oct. 10, 1924	+30	96	58	Lugol's sol. m. 30 (2 cc.) started
" 16, "	+11	80	58	Lugol's sol. m. 30 (2 cc.)
" 20, "				Subtotal thyroidectomy.
" 28, "	+11	84	58	Lugol's sol. m. 15 (1 cc.)
" 31, "	−14	72	58	
April 16, 1925	−3	76	66.5	
Sept. 3, "	−3	80	66	

Comment. — A sudden attack out of a clear sky followed shortly by spontaneous remission is of interest here. In the symptomatology, the improvement in bowel action coincident with the development of hyperthyroidism is noteworthy. There is no doubt of a close relation between intestinal rate and level of thyroid activity. As will be noted later, myxœdematous and other persons with hypometabolism often get over their constipation when thyroid is given. The present is a case where nature conducted such therapy.

Case No. 2265. *Exophthalmic Goitre in a Boy of Seven*

History. — The patient was the child of healthy non-goitrous parents, born at full term, normal delivery, and breast fed for three months, then on bottle. He gained normally until the age of seven. Three months before entry to the hospital, his mother noted a swelling in his neck and at the same time a prominence of his eyes, which gradually increased. He seemed more nervous and sweated a good deal, but had no subjective complaints whatever. He played very actively. His appetite and bowels seemed normal, and the mother had noted no tremor. He was admitted to the hospital November 15, 1923.

Examination. — This showed a well developed and nourished boy, not objectively nervous, with no tremor but with definite exophthalmos and lid lag and a moderate sized diffuse swelling of the thyroid with loud bruit. The tonsils were enlarged. The heart was rapid with loud sounds but no enlargement or murmurs were present.

The clinical examination of blood and urine showed nothing remarkable. Blood pressure was 100/50.

Management. — A diagnosis of juvenile Graves' disease was made and the administration of Lugol's solution begun. A characteristic reaction occurred as is indicated in the chart (Fig. 18). During this period, even before he had Lugol's solution, the boy did not appear more irritable than others in the ward. It was not thought advisable to operate on account of the mildness of his symptoms and the known tendency of children to outgrow the disease. He was discharged from the hospital on November 28, 1923.

On December 26, 1923, however, he was readmitted because of the development of objective nervousness and increase in metabolism, these occurring while he was taking iodine.

Physical examination at this time was as before. Five days after entry he developed what was supposed to be scarlet fever which ran a very mild course and on January 3, 1924, he was discharged.

Following this infection he improved symptomatically, but since his metabolism was mounting, he was readmitted to the hospital on January 30, 1924, for further study and treatment. The tonsils were found acutely inflamed and when this had subsided a tonsillectomy was done. X-ray treatments were also started and iodine continued. The net result of all this was a marked symptomatic improvement and a fall in metabolism. He was discharged for the third time on April 13, 1924.

When seen thereafter from time to time he appeared to be doing well. The exophthalmos and goitre decreased and he had gained weight and

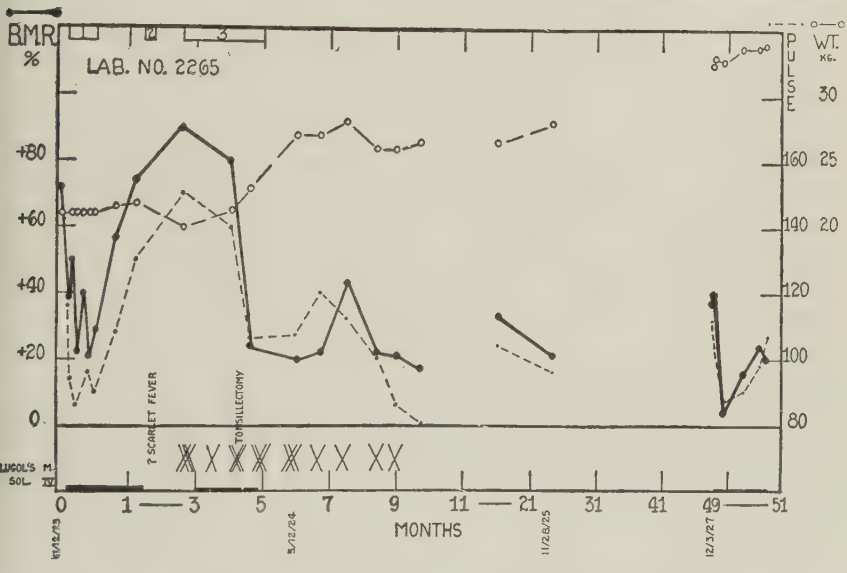

FIGURE 18. *Exophthalmic Goitre in a Boy of Seven (Case No. 2265).*

grown rapidly in height. The metabolism remained slightly supernormal, but symptoms were absent.

On March 7, 1925, there was very slight exophthalmos and a just palpable thyroid, but no symptoms whatever. His mother said he behaved like an entirely healthy boy. The metabolism remained at plus 33 per cent. On November 28, 1925, it had dropped to plus 21 per cent.

Comment. — A good example of the disease in childhood. A conspicuous feature is the mildness of the symptoms and slight interference with growth. At no time was the boy in any way incapacitated by the disease, and yet there can be no doubt that he had true exophthalmic goitre. His case, we believe, is a fair representation of the usual course of the syndrome when it occurs in children before puberty.

The rapid growth of this patient is an example of our general experience in juvenile thyrotoxics who, according to Hertz, usually are overheight for their age, when the disease is present before the epiphyses have united. This rapid growth is in sharp contrast to the dwarfism and stunting of growth in juvenile myxœdema patients and is to be explained by the synergistic action of the thyroid hormone on the growth factor from the anterior pituitary.

CASE NO. 4481. *Exophthalmic Goitre with Diarrhœa an Important Early Symptom and with an Intercurrent Throat Infection*

History. — A twenty-eight year old, married, Italian immigrant, mother of five children, entered the hospital with the story that three months before she had begun to notice slight dyspnœa on effort, palpitation and easy fatigableness; none of these, however, was severe enough to stop her doing her daily work as a spinner in a woolen mill. After two months of this, she observed that her eyes were becoming prominent, and a few days later she was seized suddenly with a severe diarrhœa. Bowels had previously been acting quite normally. On the day the diarrhœa appeared, there were about twenty stools, watery but containing no blood or mucus. For three weeks this continued unabated, but by the fourth it lessened somewhat. During the first week of it there was nausea and vomiting as well.

There were griping pains the first three days of the diarrhœa but not since. She gave up work the day the diarrhœa commenced and had been unable to return. A few days after the onset of diarrhœa, she noted a swelling at the base of her neck and painted it with iodine, in spite of which the swelling increased. The symptoms all had been intensified since the diarrhœa appeared. There was marked nervousness and irritability. She would jump at slight noises, and her heart would pound very hard. She would tremble, and although she had always been a good walker, found that she could barely "drag one leg after the other". She lost three or four kgs.

The appetite had been poor, and she had felt cold and had perspired but little since the beginning of her illness. For two weeks before entry there had been polyuria. The past history gave no clue to the origin of her disease.

Examination. — This showed a well developed and nourished woman,

somewhat apprehensive but by no means unduly restless. There was slight exophthalmos and lid lag, moderate, diffuse, smooth enlargement of the thyroid with loud bruit, warm moist skin and slight fine tremor of the fingers. The tonsils were large and cryptic; heart action was rapid and violent.

The routine laboratory work showed nothing remarkable.

Management. — The patient directly after admission to the ward, January 25, 1927, developed sore throat and headache, and the following day a fever. The diarrhœa stopped. The tonsils and throat became œdematous, and an ulcerated area covered with grayish membrane appeared in each tonsil. Diphtheria bacilli were obtained in culture, but these later proved to be avirulent. Antitoxin, however, was given. The clinical chart shown in Fig. 19 tells the story.

As soon as the throat infection cleared, she felt remarkably well, and the thyrotoxic manifestations appeared to be slight. Lugol's solution was started and a response having been obtained, subtotal thyroidectomy was done. This was followed by an uneventful recovery.

The metabolism data were as follows:

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
Jan. 26	+ 98	144	47.9	Temperature 101.5
" 27	+ 83	132	48.3	Temperature 101.
" 29				Lugol's sol. m. 45 (3 c.c.) started.
Feb. 7	+ 19	92	48.3	Lugol's sol. m. 45 (3 c.c.).
" 8				Subtotal thyroidectomy.
" 18	− 4	72	47.5	

Comment. — This case is of interest for two reasons. First the manner of onset, second the response to infection. With regard to the first it may be pointed out that the onset was gradual, but after two months there was apparently an acute exacerbation of thryotoxicosis with diarrhœa as a prominent symptom. Diarrhœa, as we have pointed out, is a well recognized manifestation of Graves' disease, though in our analyzed series it occurred in but 29 per cent. It frequently starts very suddenly as in this patient and often ceases in similar fashion. There is often no pain with it. Here there was a little at the start. It seems fair to attribute it directly to the effect of hyperthyroidism, which as we have seen in this connection often accelerates intestinal activity, but why some patients with Graves' disease have it and others do not is unknown.

Patients with exophthalmic goitre not infrequently appear to be improved after acute infections. In this case there was perhaps improvement and certainly no aggravation following the throat infection.

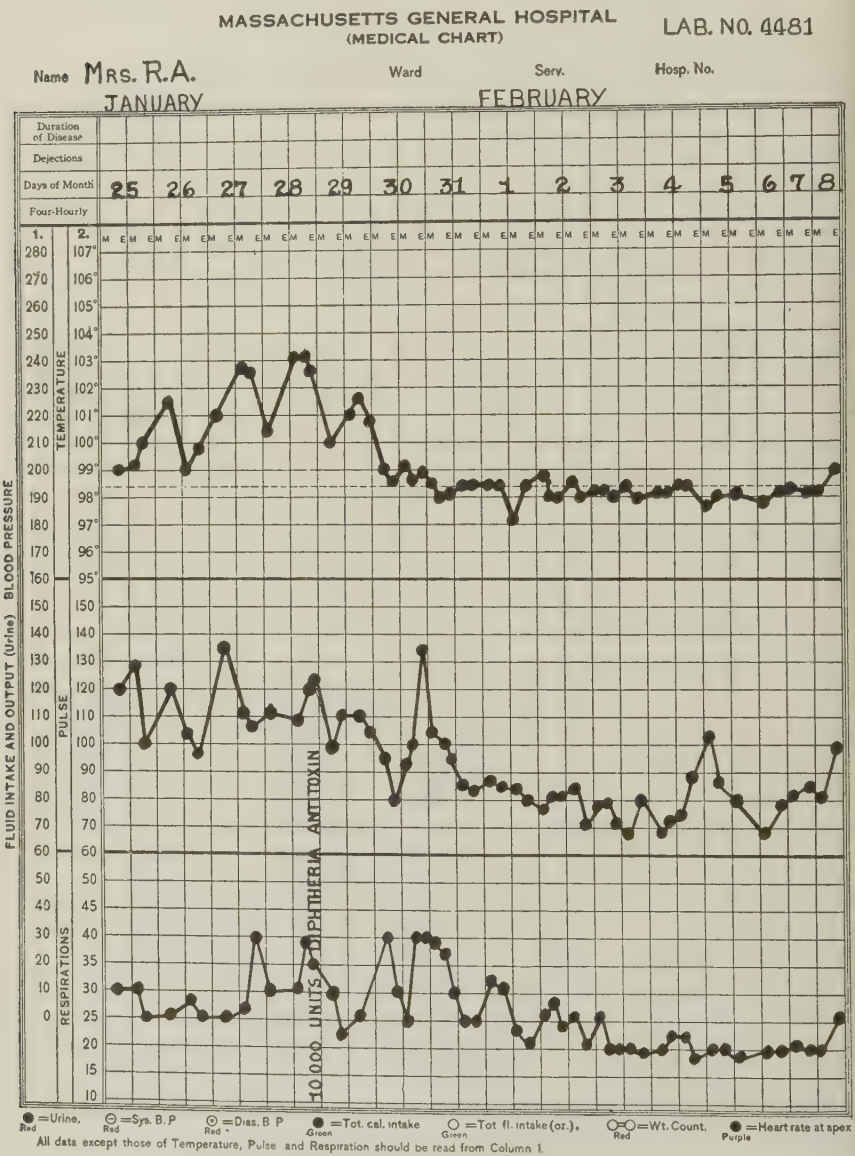

FIGURE 19. *Exophthalmic Goitre. Clinical Chart in Case No. 4481.*

The metabolism and pulse were quite elevated, but fear would account for a considerable portion of this, perhaps 20 to 30 points, and symptomatically there was absolutely nothing to suggest a thyrotoxic crisis. The injection of horse serum was also without ill effect or even serum sickness.

Case No. 4828. *Exophthalmic Goitre in a Girl of Fourteen with Vomiting an Important Symptom*

History. — A Boston born child of Italian parents was admitted to the hospital with the story that she had been ailing for about four months, the chief symptoms being dizziness, nausea and vomiting. They began insidiously but had got progressively worse, especially during the last month. Each morning the patient would feel dizzy and sick at her stomach and then vomit greenish, slimy, sour material. The sour taste stayed in her mouth all day, and she would be nauseated after the other meals as well. In addition, there was weakness, polydipsia and nearly constant headache. The appetite was increased, but she believed that only a small portion of her food had been retained.

There was considerable lassitude but also restlessness. She would thrash about in bed and be unable to get to sleep. There was increased sweating but no dyspnœa or palpitation. She had lost about 3.5 kg. in a month. The catamenia had begun two years before and remained regular throughout the illness. No exacerbation of symptoms occurred with the periods. No exophthalmos or goitre had been noted by her family. There was nothing in the past history that seemed important.

Examination. — This showed a restless girl with flushed face, of good size and fair nutrition. There was slight exophthalmos and lid lag and a soft symmetrical, rather small goitre, with loud bruit. The skin was hot and moist, and her fingers showed a fine tremor. The physical findings were not remarkable in other ways. Clinical examination of the blood and urine revealed no abnormality. The blood pressure was 130/90.

Management. — There was adequate evidence for a positive diagnosis of exophthalmic goitre. She was, therefore, put to bed and given Lugol's solution. When the metabolism had dropped to normal, a subtotal thyroidectomy was done. She had a secondary hæmorrhage following this and later sepsis in the wound which gave her fever for a week. She also showed a postoperative subnormal metabolic rate for which she was given thyroid.

The blood pressure dropped with the metabolism to 110/60 on June 14.

The data were as follows:

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks.
June 10	+49	128	49.3	Lugol's sol. m. 30 (2 cc.).
" 18	+8	101	47.3	Lugol's sol. m. 30 (2 cc.).
" 22				Subtotal thyroidectomy.
July 2	−31	98	46.5	Lugol's sol. m. 20 (1.3 cc.).
" 6	−22	78	47.1	Thyroid grains 6 (0.4 gm.).

Comment. — The case is interesting because of the early age at onset, but in a girl past puberty it more closely resembles the adult than juvenile type. It is shown chiefly because of the atypical symptoms which if considered alone might lead to a wrong diagnosis. That sometimes nausea, vomiting, dizziness, and headache may be presenting symptoms in Graves' disease is important to remember. The fall in blood pressure as metabolism declines is well shown and representative of a usual trend.

CASE NO. 4347. *Exophthalmic Goitre. Insidious Onset Following Pregnancy, Aggravated During Next Pregnancy*

History. — A housewife of 28 from Wilmington, Mass., entered the hospital November 19, 1926, complaining of goitre. She had had three children, all three living and well, and no miscarriages. The youngest child was born two years before entry, and up to that time the patient had felt very well. Since then, however, she had felt tired practically all the time and had frequent, dull occipital headaches. Along with this there had been an increase in appetite but a loss of 13 kgs. A year before entry a mid-line goitre was noted for the first time, and seven months later protrusion of the eyes. During the last four or five months she had also complained of slight dysphagia and "consciousness of her throat", palpitation and tachycardia, increased sweating, falling of her hair, trembling, and definite increase in irritability. For three months she had had amenorrhœa and morning vomiting, and for one month dyspnœa on effort and slight orthopnœa.

An emotional factor possibly playing a rôle in causation of symptoms was found in a marked marital incompatibility. The headaches she had had off and on since girlhood, but they had been worse in the last two years.

Examination. — This showed a somewhat nervous, well nourished woman (a portion of her weight lost had been regained in last 3 months), with moderate prominence of eyes and lid lag, a symmetrical smooth fullness

of the thyroid with bilateral bruit but no palpable thrill, and a fine tremor of the fingers. The skin was warm and moist. The introitus was blue, the cervix soft, and the uterus enlarged to the size of an orange. The areolæ of the breasts were prominent. Blood pressure was 130/80 and urine and routine blood examinations not remarkable.

Management. — A diagnosis of exophthalmic goitre and three months' pregnancy was made and operation decided upon, because it was believed she presented a good risk and that the continuation of her thyrotoxicosis was doubly undesirable on account of the pregnancy. Lugol's solution was therefore given and subtotal thyroidectomy done. The data were as follows:

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
Nov. 22	+41	124	46.4	
" 23				Lugol's sol. m. 15 (1 cc.).
" 26	+40	100	47.7	Lugol's sol. m. 15 (1 cc.).
" 30				Subtotal thyroidectomy.
Dec. 8	+16	72	47.4	Lugol's sol. m. 45 (3 cc.).
Jan. 19	−7	77	52.1	" " m. 20 (1.3 cc.).
Mar. 8	0	94	55.5	" " m. 5 (0.3 cc.)
May 25				Child born, full term.
June 15	+12	88	52.7	

Comment. — From the point of view of the natural history of the disease this case illustrates a rather insidious onset apparently starting during a puerperium with a rather mild course for a year and a half, then an intensification of symptoms during which she got pregnant. This last pregnancy did not appear to be the cause of the exacerbation for the latter began first. It is of interest that the therapeutic program followed not only relieved the thyrotoxicosis but enabled her to go through pregnancy normally and give birth to a healthy child. When last seen she had no symptoms or signs except moderate residual exophthalmos. This is often the last sign to go and it sometimes never goes.

Case No. 4392. *Mild Exophthalmic Goitre Developing in Patient with Previous Colloid Goitre*

History. — A girl of 17 from central Massachusetts entered the hospital on December 9, 1926, for trembling of her hands, palpitation

of the heart especially at night, twinges of pain over the heart especially on walking, shortness of breath on exertion, asthenia, and nervousness. All these symptoms had been developing over a period of about six months. For two months the eyes had been becoming prominent. There had not been loss of weight or increased sweating but the appetite was increased.

She had had a symmetrical goitre from the time of her first catamenia at the age of fourteen. This had shown a tendency to fluctuate in size increasing with each succeeding period, but was unproductive of other symptoms.

The past history was unimportant, but it is of interest that two sisters also had what appeared from her account to be simple goitres.

Examination. — This showed a somewhat excited girl with slight exophthalmos, moderate symmetrical goitre with smooth surface of firm consistency with faint bruit over the left lobe. The skin was warm and moist and there was slight tremor of the fingers. The other physical and laboratory findings (except basal metabolic rate) were not remarkable.

Management. — She was given Lugol's solution and reacted in the characteristic way. When the symptoms were gone a subtotal thyroidectomy was done. The data were as follows:

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks.
Dec. 11	+42	136	58.1	Lugol's sol. m. 15 (1 cc.).
" 17	+13	88	57.3	" " "
" 21				Subtotal thyroidectomy.
" 29	−1	92	56.2	
Jan. 26	−20	76	60.5	Pot. iod. gr. 5 (0.3 gm.).
Apr. 1	+1	80	58.7	Lugol's sol. m. 5 (0.3 cc.).
July 2	+2	76	58.0	" omitted.

The histologic examination of the thyroid, although it showed hyperplastic epithelium with papillary infoldings characteristic of exophthalmic goitre, also showed a larger amount of colloid than is usual in that disease even after iodine administration.

At the time of her low metabolism on January 26, 1927, she had no symptoms of myxœdema and felt very well, her face appeared rather full and her speech was slow. On July 2, 1927, she was essentially well; very slight exophthalmos remained.

Comment. — A very mild type of exophthalmic goitre developed in a

girl with previous colloid goitre. The two are probably unrelated. It is of interest to note that the case originated in a part of Massachusetts that is definitely, though slightly, goitrous.

CASE NO. 3947. *Exophthalmic Goitre with Sudden Onset Following Severe Fright*

History. — A Connecticut business man was referred to one of us (J. H. M.) by Dr. Henry S. Plummer in May, 1926. He was at that time 49 years old. Eight years previously (age 41), having before that been absolutely well, he sustained a very severe fright. He allowed a little girl of whom he was fond to mount his saddle horse. The horse broke loose and bolted, throwing the child. He ran after the horse, up two hills, about half a mile, and met some boys who said they saw the girl "thrown from her horse and guessed she was dead". As a matter of fact, she was not seriously injured. Within the week, the patient noted rapidly developing and extreme nervousness; he became quite unreasonable, both of these qualities being entirely new in him. He also got very shaky in both upper and lower extremities; his knees would give way on going up stairs and his hand trembled so on writing that his bank refused to honor a check he had signed, not recognizing his signature. Exophthalmos also developed rapidly, together with increased sweating and marked palpitation. His heart pounded so hard that his bed clothes would rise and fall with each heart beat. His appetite increased and his weight fell. No goitre was noted then or subsequently.

He went to the Mayo Clinic and three months from the time of onset had ligation of the superior thyroid arteries followed by subtotal thyroidectomy.

Comment. — The operation at Rochester was on July 19, 1918. He was not seen in our Clinic until May 1, 1926. He had improved rapidly after operation but later developed some important residual manifestations, of a sort which will be discussed fully in the next chapter. His early history is presented here as a typical instance of fulminating exophthalmic goitre following fright. These cases are occasionally seen by anyone caring for any great number of patients with thyroid disease. How the psychic trauma acts is quite unknown, but that it plays some rôle seems unescapable. It is also of interest that, though in all other respects typical Graves' disease, there never was in this case a goitre large enough for the patient to notice. The pathologic report from the Mayo Clinic, however, describes the parenchymatous hypertrophy characteristic of exophthalmic goitre.

Another point worthy of mention is that again in a man we see the disease in a severe form. As stated earlier, repeatedly we have been impressed that for the most part men either have this disease severely or not at all, in contrast to women who often have it mildly. Compare case No. 4392.

Case No. 4383. *Exophthalmic Goitre. Effect of Iodine on Intense Nervous Symptoms.*

History. — A Nova Scotian housewife of 43 began to have symptoms one year before entry to the hospital on December 6, 1926. She had been well previously, but had been through considerable strain. A brother had died suddenly and there had been acute financial difficulty owing to her husband's being thrown out of work by a strike. Furthermore, the family was obliged to move from a town that was congenial to her to one that was not.

The first symptoms noted were rapid loss of weight (9 kg. in 1 month) and much trembling. Her hands would shake so that it was difficult to hold things. She trembled in like manner all over. She said it was not a twitching but rather a coarse tremor. It was not improved by resting, in fact she thought aggravated. A gneral nervousness also appeared, and a swelling in the right side of her neck. After six months of this trouble she got two months at the seaside and improved quite markedly, including a gain in weight and a decrease in the neck swelling. At the end of this vacation, however, all the symptoms returned in more severe form. The neck increased in size again and her heart began to beat very violently. Her appetite became excessive. Three months before entry the family moved from Nova Scotia to a coast town of Massachusetts where she was very homesick. This was followed by a still further aggravation of all symptoms. A pronounced asthenia appeared, also dyspnœa on effort. The heat became very oppressive and her face was frequently flushed. Sweating was much increased. The swelling in the neck underwent further increase. The bowels had been regular with no diarrhœa. The catamenia had been unchanged. She had noted no change in appearance of her eyes, but friends had observed some prominence within the last few weeks, and even five months before her sister had thought that she had a "wild look in her eyes".

Examination. — This showed a woman nervously unstrung and highly emotional, restless, fidgety, and subject to frequent crying spells. There was slight exophthalmos without other eye signs. A slight, diffuse, firm, symmetrical fullness of the thyroid with loud bruit was present. The

skin was moist and showed dermatographia. The heart was not enlarged but was rapid with a systolic murmur at the apex. There was moderate tremor. The urine was not remarkable. The blood showed a slight secondary anæmia: 4 to 5 million red cells, 75% hemoglobin. There was leucopenia of 4800 with 58% polynuclears, 25% lymphocytes, and 17% large mononuclears. Blood pressure was 125/50.

Management. — The case was clearly typical exophthalmic goitre with nervous symptoms especially marked. Lugol's solution was started in doses of m. 45 (3 cc.) per day. The response was immediate and remarkable. The nervousness ceased. The mental depression and crying departed and the whole psychologic picture shifted in the direction of normality within 48 hours. At entry she had shown a sign described by Plummer: a marked erythema over the elbows. Under the effect of Lugol's solution this rapidly disappeared. On the eighth day of Lugol's, she was in a satisfactory remission, and subtotal thyroidectomy was done. The progress is indicated in the following data:

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
Dec. 9, 1926	+88	130	49.9	Lugol's sol. m. 45 (3 cc.) started.
" 15, "	+37	105	49.9	Lugol's sol. m. 45 (3 cc.).
" 17, "				Subtotal thyroidectomy.
" 24, "	+13	80	47.5	Lugol's sol. m. 15 (1 cc.),
Jan. 21, 1927	−16	61	54.7	Lugol's sol. omitted.
Feb. 1, "	−7	62	56.9	

The convalescence was uneventful and she was discharged from the hospital on December 27, 1926. She took Lugol's m. 15 (1 cc.) for a fortnight after this and then omitted it. At the end of a month she had some puffiness of the face, a little weakness, slight hypometabolism, but no nervous symptoms.

Comment. — This case represents a type seen frequently in women, very rarely in men, in which the subjective nervous phenomena seem more marked than the intensity of the thyrotoxicosis as judged objectively would lead one to expect. Their very prompt control by large doses of iodine is striking and important. The red elbows described by Plummer are probably not merely due to thrashing about but rather to the latter plus an increase vasomotor instability. Both of these are abolished by iodine.

CASE NO. 3260. *Exophthalmic Goitre with Toxic Crisis*

History. — A twenty year old, single, Russian Jewess entered the hospital May 20, 1925. She had had measles as a child and frequent attacks of tonsillitis until tonsillectomy one year earlier. She had come to the United States three years earlier and had been in excellent health until three months before entry, at which time a swelling in the neck was first noted. Following this in close succession other symptoms developed: marked increase in irritability, profound asthenia, increased sweating and appetite, also headache, dyspnœa, insomnia, polydipsia, and nocturia. These all increased rapidly in intensity and her expression became very staring. A marked tremor developed and she had lost about 14 kgs. in weight. For four weeks she had been in bed. No causative factors, psychic or other trauma could be discovered.

Examination. — This showed an extremely restless and excited young woman thrashing about, with wildly staring expression though the exophthalmos was slight. She was flushed, cyanotic, hyperpnœic and vomiting; the breath smelled of acetone. The skin was hot and dry. The lips were dry and cracked. The heart action was rapid and violent. The heart was enlarged with a loud harsh systolic murmur at the apex. The extremities showed a very marked coarse tremor. The urine was not remarkable. The blood showed a leucocytosis of 15,000 with 90 per cent. of polynuclears.

Management. — The patient was obviously in an acute toxic crisis of Graves' disease. There was in addition evidence of severe dehydration and acidosis. She was put to bed at once, fluids given freely intravenously and subpectorally, as she could retain none by stomach or bowel. Morphia was required the first night. A basal metabolism test the next day showed a rate of plus 119 per cent. Ninety minims (6 cc.) of Lugol's solution were given on this day and continued for eight days, then reduced to thirty (2 cc.). There was a very rapid and marked improvement. Even by the second day on Lugol's solution, her symptoms were vastly better and the entire picture changed. The pulse was found to vary considerably and palpitation was troublesome at times, and although her heart was not fibrillating, quinidine was tried for a time with no striking effect. The progress is shown in the chart Fig. 20.

It was felt that early operation was essential and hemithyroidectomy was done on June 8, 1925. Four hours after operation a severe secondary hæmorrhage occurred causing pallor and elevating the pulse to 140. She improved slowly after this, though many thyrotoxic symptoms remained. On July 3, 1925, she was discharged to a convalescent home.

On September 8, 1925, she was readmitted. In the interval she had taken Lugol's solution steadily but in spite of this at no time had been free from toxic symptoms. The remaining lobe of the thyroid had enlarged somewhat, so after a period of rest and further iodine, on September 25, 1925, a second thyroidectomy was done.

Following this for a time she was better. Her symptoms never entirely disappeared, palpitation being especially troublesome, but her metabolism fell and she gained a lot of weight. In March, 1926 this

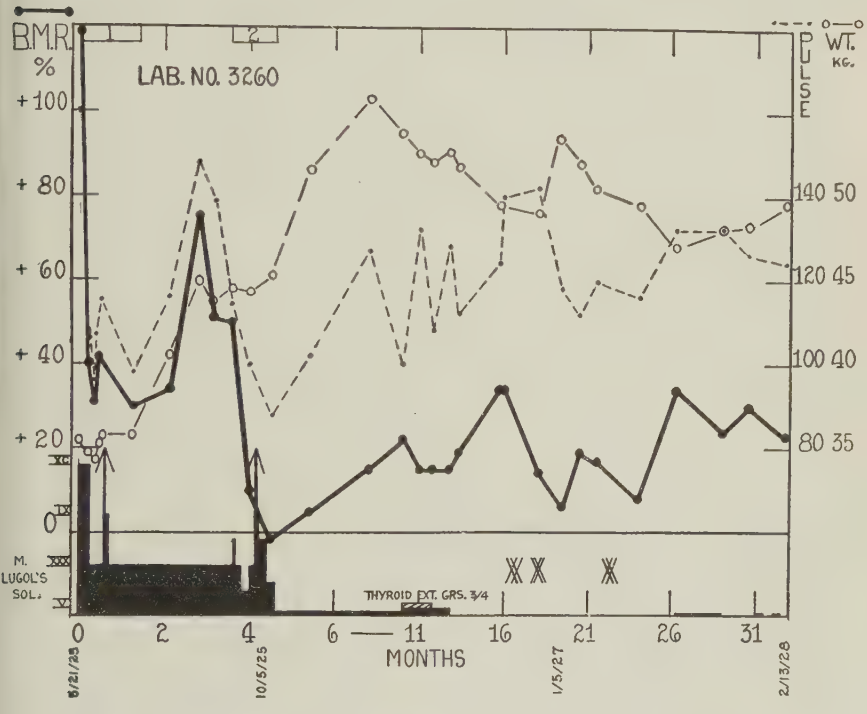

FIGURE 20. *Exophthalmic Goitre (Case No. 3260).* Thyroid administration in this and subsequent charts shown thus, ▨ at bottom.

had reached such a point that some thyroid was tried cautiously along with Lugol's solution, which had never been omitted. The thyroid produced little weight loss and increased her symptoms, so after two months' trial it was omitted. On June 15, 1926, Lugol's was omitted.

In the autumn of 1926 there was a definite recrudescence of thyrotoxicosis relieved somewhat by X-ray treatment.

Comment. — There are many instructive features in this case, although

it is presented chiefly to illustrate a typical toxic crisis and the immediate correction thereof by iodine, precisely as Plummer has claimed. This effect on the symptoms was noticeable within 24 hours. Operation in such a state without iodine would have been exceedingly dangerous, and the state itself without operation in the pre-iodine days would very likely have proved fatal.

The subsequent course illustrates the difficulties one sometimes encounters. The therapeutic program should have been adequate to render her symptom-free, but it never did. Even when but a slight remnant of thyroid remained, she managed to get definitely thyrotoxic. Lugol's solution was less efficacious in the relief of these residual phenomena than in most of our other cases. The heart behaved in a very unusual way from the start, bearing very little relation to metabolic rate, but we never were able to identify any organic heart disease other than thyroid. It was suggested that she had paroxysmal tachycardia, but the jumps in rate were hardly exact enough to warrant that diagnosis.

When least thyrotoxic, psychologic examination indicated that she was a psychasthenic of low intelligence, undoubtedly congenitally so. What rôle this may have had in the genesis of her Graves' disease defies solution.

Cases No. 25 and No. 4792. *A Mother and Daughter with Exophthalmic Goitre*

Histories. — Mrs. L., a Lithuanian housewife, resident in Haverhill, Mass., developed moderately severe exophthalmic goitre in February, 1915. She was treated in the Massachusetts General Hospital clinic by X-ray and recovered. The early data were reported by Means and Aub in 1919[51]. Since then she has been observed from time to time and has remained well. On February 26, 1925, she presented no evidence of Graves' disease of any kind and was working hard each day. Her metabolic rate was plus 5 per cent., her pulse 64, her weight 79.2 kg. She was too fat. When first seen in 1915 she had weighed 50.5 kg.

On May 25, 1927, she was seen again. She still felt perfectly well and had lost 7 kg. as a result of diet reduction supervised by our dietitian. At this time, however, she brought in her daughter Mrs. B. (No. 4792), age 24, presenting a typical picture of exophthalmic goitre of moderate severity which had been developing over a period of three months. She was given iodine and responded in the usual manner. A subtotal thyroidectomy was done and she made thereafter an uneventful recovery.

CASE NO. 13481. *Exophthalmic Goitre Without Treatment and Supervening Myxœdema. Exhaustion of Thyroid*

A 28 year old graduate nurse was first seen by Dr. Richard C. Cabot in 1898 with a definite picture of exophthalmic goitre. She was described as having unmistakable exophthalmos and a neck circumference of 18 inches. Because of the high operative mortality which she had observed, while she was in training school, she refused surgical treatment and took up "faith healing". In 1915, at the age of 43, she was admitted to the hospital for treatment of pleurisy with effusion and was described as having a "thyroid gland which was only slightly prominent" but a moderate degree of exophthalmos persisted at that time. She at no time received medication directed toward her thyroid.

In 1934, at the age of 64, she was readmitted to the Massachusetts General Hospital with the following complaints; progressive weakness and unsteadiness of gait of about 1 year's duration, increasing dyspnœa on exertion with occasional palpitation and precordial ache, intolerance to cold, increasing drowsiness and retardation in physical work, irritability, diminution in acuity of sight and hearing, paresthesiæ of hands and feet, a gain in weight of 12 pounds in one year and the appearance of puffiness of her face and hands. She also noted increasing distension of her abdomen and required vigorous catharsis for bowel regularity.

Examination showed an elderly woman, who was slowed up in her psycho-motor reactions. Her hearing was very poor. Her face and eyelids were puffy, and her cheeks were full. Her hair and skin were dry, and her extremities were cold. She had no axillary hair, and her pubic hair was scant. Her eyebrows were thin. Moderate exophthalmos was present. No lid lag was elicited. Her eyes converged poorly in accommodation. Her tongue was large and beefy, and her speech was slow, hoarse and thick. No goitre or thyroid tissue could be palpated. Her heart was moderately enlarged (confirmed by x-ray), and her blood pressure was 170/100. Reflexes were sluggish. The urine was normal. Specific gravity varied between 1.010 and 1.025. Blood cholesterol was 442 mgm./100 c.c. Basal metabolism readings were minus 30, 29, 31, and 30 before treatment. Electrocardiographic study showed T waves typical of myxœdema.

Management: The patient, therefore, was obviously quite typically myxœdematous. She was started cautiously on one half grain daily of U. S. P. thyroid because of her age and the history of anginoid pain in order to avoid the danger of a coronary accident. When it was seen that she tolerated thyroid well, the dosage was gradually raised to two grains

daily. On the latter dosage she became free from all her myxœdematous complaints and lost three kilograms in weight.

Comment: We have in this case a patient who over a long period of time, with no treatment whatsoever directed toward her thyroid overactivity, spontaneously developed typical myxœdema. The persistence of exophthalmos is of considerable interest, and it is quite likely that the prolonged stimulus to her thyroid, whatever it may have been, finally caused an exhaustion of the thyroid epithelium to such a degree that sufficient thyroid hormone was not available for normal metabolism. If physicians could analyze the sequence of events in such cases, the reproduction of it might hold the possibility of a medical cure of the disease. The work of Hertz and Kranes[62] in rabbits showed that prolonged stimulation of the thyroid with thyrotropic materials derived from the anterior pituitary caused histologic evidence of depression of the thyroid function which they chose to term the "exhaustion phenomenon". It would appear that in this clinical case we have an example in the human of thyroid exhaustion.

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CHAPTER VI

EXOPHTHALMIC GOITRE (CONT.)

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Treatment

In discussing the treatment of exophthalmic goitre one should admit at once that the disease shows a definite tendency to spontaneous remission and self-limitation. Therefore in judging of the efficacy of any form of therapeutics one must remember these tendencies, and must duly consider their possible rôle in any given improvement.

The ideal treatment of any disease is through the removal of the cause. The cause of Graves' disease is unknown; treatment therefore falls into the category of the symptomatic. In the production of symptoms, as we have seen, the thyroid is of

great or small importance in the varying views of different writers. The majority hold the view that it is responsible through its secretion for the chief symptoms and signs of the disease. The most important methods of treatment, therefore, have been directed towards this gland and seek to depress its functional activity, the idea being that, although the mysterious cause of the disease may not be removed, the organ responsible for the chief manifestations is held in check, and symptomatic relief brought about. Such methods of treatment are the various types of thyroidectomy and irradiation by X-ray or radium, together with some less important procedures such as the injection of boiling water and ligation of thyroid vessels.

There are also certain general measures that will require comment, chief among which are rest and a number of drugs. Of the latter iodine alone has any outstanding importance.

It is natural in a disease of unknown cause and in one for which the specific remedy has yet to be discovered, that modes of treatment will vary from place to place and time to time. It has been the policy in the Massachusetts General Hospital clinic at all times to employ the program which seemed most likely to benefit each individual patient. Our views as to what constitutes the best therapeutic program have changed repeatedly. This is well illustrated in the analysis of how we have actually treated our cases in three four-year periods, which is shown in the following table.

In the first period, it will be noted that there is about an even split between surgery (41.5 per cent.) and X-ray (39.5 per cent.), with 19 per cent. of the patients receiving both. In the second period surgery has become less popular (32 per cent.) and X-ray more so (51 per cent.), while 15.5 per cent. had both. In the third period X-ray has dropped to 9.5 per cent. and

	X-ray only	X-ray combined with Surgery	Graded Operation*	One stage Subtotal	Ligation only	Iodine only
Preiodine	%	%	%	%	%	%
1915–18	39.5	19.0	32.0	8.0	1.5	0
1919–22	51.0	15.5	22.0	8.5	1.5	1.5
Postiodine						
1923–26	9.5	6.5	14.0	60.5	0	9.0
1927–31	3.3	0	3.3	86.1	0	7.3
1932–35	0.6	0.3	7.1	90.5	0	1.5

* Includes a few cases in which the operative procedure was not carried further than hemithyroidectomy.

surgery risen to 74.5 per cent., with 6.5 per cent. more that had both. Ligation of arteries as a sole measure was never done except in isolated cases and was not done at all after 1922. The type of surgical program too shows a change. In the last period, owing to preliminary preparation with iodine, there is a great increase in the percentage of one stage thyroidectomies.

In the fourth period, 1927–31, we note the great increase in percentage of cases treated by subtotal thyroidectomy. Graded operations and X-ray treatment were relegated to comparatively minor places in the therapeutics of the disease.

In the fifth period, 1932–35, it is evident that a slightly greater use of graded operations (no ligations) was made and that X-ray was used in only 0.6 per cent. of the cases as the sole form of therapy.

The policy of the clinic in the period of 1936–39 can be predicted from the tendency already manifested. A swing of the pendulum back to stage operations (hemi-thyroidectomy for the most part), an increasing use of X-ray in the poorer risks for operation and a growing field for treatment by iodine alone in cases selected by recent criteria as suitable for medical management seems likely.

We are learning to classify our patients as to probable risk of operation as follows:

A. GOOD RISKS: This class will include the ordinary non-toxic goitre and uncomplicated toxic goitre of very mild intensity.

B. MEDIUM RISKS: This class will include the ordinary case of uncomplicated moderately severe toxic goitre.

C. POOR RISKS: This class will include those patients who present any of the following criteria of inability to stand operation well: 1. Poor or absent iodine response. 2. Rising B.M.R. 3. Presence of complications, chiefly cardiac. 4. Extreme intoxication, indicated by either very high B.M.R. or severe symptoms on iodine, crisis status. 5. Old age. 6. Psychotic manifestations. 7. Marked malnutrition. 8. Marked myasthenia or muscle atrophy.

Between the policies in the first period and those in the second there is no radical change. X-ray therapy gained somewhat in popularity, because doubtless it had established its effectiveness and was clearly safer than surgery. The third period, however, shows an extraordinary shift; X-ray rapidly drops out of use and one stage surgical operations come to the fore. This change is entirely due to Plummer's[1] discovery of the iodine remission, by which the risk of any type of operation is largely wiped out, and hence the need for graded operations is greatly reduced. Taking advantage of the iodine remission the surgeon now can do safely an adequate operation in one stage, when in the past often it had required several. The popularity of a therapeutic procedure does not of necessity prove its worth; yet in the main if one form of therapy is widely used to the exclusion of others, it is because it is more

effective. We believe the above table tells a fairly true story of the relative effectiveness of such therapeutic procedures as we have at our disposal to-day, and offers sound advice to the practitioner on the selection of a proper therapeutic program. Our experience with these several methods will be discussed in detail.

X-ray Therapy

The X-ray has long been known to have a withering effect on various glands, so theoretically at least its trial for that purpose upon the thyroid in Graves' disease is altogether reasonable. We have been unable to discover who first used it for that purpose. F. H. Williams[2] and Pusey and Caldwell[3] were among the pioneers (1902 and 1903). Another early worker in this field was Pfahler[4], who in 1908 was able to collect fifty-one cases from the literature, forty-two of which showed good results after X-ray treatment. Since then a considerable literature has been built up, much of which comments favorably on the supposed beneficial effect of X-ray. The treatment was used by Holmes[5] at the Massachusetts General Hospital as early as 1914, and up until 1923 was given an extensive and carefully controlled trial. A preliminary report was made in 1917 by Means and Aub[6] and a more detailed one in 1919[7]. The conclusions reached at that time based on a series of fifteen patients treated by X-ray alone were that the results of X-ray therapy compared favorably with the surgery of that period which was ordinarily limited to hemithyroidectomy. The risks of operation were greater then than they are to-day, and the operation a greater ordeal, as it was generally done in several stages. In addition, therefore, to the apparent direct benefit of X-ray therapy, there were the added points in its favor that it carried no immediate mortality and that pa-

tients need not be bedridden while receiving it. We freely admitted then, as we have subsequently, that a certain minority of the cases derived no benefit. It was thought at that time that the best program was an adequate course of irradiation followed, if necessary, by operation, if satisfactory improvement had not been secured by X-ray alone.

In 1923 Means and Holmes[8] reported a second series of forty-four cases of exophthalmic goitre treated by X-ray therapy and made a further report on the end results of the first series. Of the forty-four new cases sixteen showed little or no improvement, while twenty-eight, or a little less than two-thirds, showed

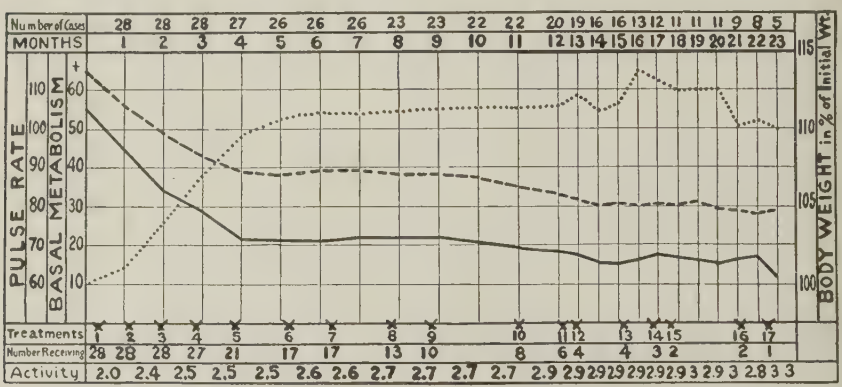

FIGURE 21. *Exophthalmic Goitre.* Effect of X-ray treatment. Composite chart of 28 cases. Solid line, basal metabolism; interrupted line, pulse; dotted line, weight.

definite improvement. Other writers have reported better results[9]. The general nature and rate of this improvement may be inferred with fair accuracy from the metabolism, pulse and weight curves, composites of which are shown in Fig. 21.

In this it appears that a steady improvement occurred in the first four months after four to five treatments, and then a very slow one during the subsequent year. The results after five to six years in the first series were that out of fifteen, three had died, three had disappeared, and of the remaining nine, seven

were apparently well and two still slightly toxic but improved. On the basis of all these observations it was concluded in 1923 that about two-thirds of the cases of exophthalmic goitre can be improved by X-ray therapy, and that this mode of treatment has a definite place in the therapy of Graves' disease. It should be noted, however, that in only about one-third of the patients was the metabolic rate restored permanently to limits within normal. Another third, although definitely improved, remained somewhat thyrotoxic and still showed symptoms of the disease, but in a modified form. These improved cases constituted a difficult problem in regard to further treatment. They ordinarily felt reasonably well and were restored to full economic activity, so that they were unwilling to undergo operation. At the same time, undoubtedly they were receiving more or less progressive damage from continuation of the toxæmia. This group of cases perhaps presented a more serious objection to X-ray treatment than those in which radiation frankly failed, as the latter group ordinarily were willing to undergo operation. Since 1923 very few new cases have been treated by X-ray because of the advent of subtotal thyroidectomy during iodine remission.

The method used up to 1925* was to expose three areas, two thyroid and one thymus for two-thirds of an erythema dose every three weeks. Coolidge tubes were used with an interrupterless machine. The parallel spark was approximately eight inches. The rays were filtered through 4 mm. of aluminium and 1 mm. of leather. The target-skin distance was 8 in. in the earlier cases, in the later 10 in., and in some a 16 in. distance was used. The time interval between treatments was usually three weeks, occasionally two weeks. As a rule patients were

* Since 1925 we have used deep therapy giving two-thirds of an erythema dose over one area and repeating if necessary in six to eight weeks. (200 kilovolts., 50 cm. distance, .5 mm. copper filter, 4 milliamperes.)

treated on an ambulatory basis, frequently with no other treatment of any sort, and continuing their usual activities. The optimum number of treatments cannot be fixed definitely. Some of the earlier cases received as many as eight treatments, but relatively early in the study it was found that if four or five treatments did not give a satisfactory improvement, further irradiation would not do so; therefore in 1923 Means and Holmes stated definitely that "prolonged roentgen-ray treatment in patients showing no response is undesirable". This does not mean that a second course of X-ray should not be given in patients showing a response to a first, but who subsequently have a return of thyrotoxicosis. For the treatment of such relapses X-ray has often been used, sometimes with success (as in Case No. 1569).

The improvement to be expected in the successful cases is both subjective and objective. The nervous phenomena tend to diminish in intensity, though, as we look back now in the light of Plummer's work, we cannot say that there was any sudden subsidence in the peculiar Graves' manifestations that one sees after the use of Lugol's solution; the improvement was much more gradual. The symptoms taken as a whole, both the nervous and the circulatory, plus the metabolism and pulse rates and the behavior of the body weight, were our chief criteria for saying whether improvement truly had taken place. There was, however, one thing that impressed us early, and which we still believe important, and that is that while some patients got no benefit by X-ray, we observed none apparently rendered worse by it.

That the thymus plays an important rôle in exophthalmic goitre has long been believed. Halsted[10], for example, who in 1914 delivered a Harvey Lecture on the subject, reports both from his own experience and from the literature cases of exoph-

thalmic goitre in which the operation of thymectomy was followed by remarkable improvement. He states that autopsies show the thymus persistent in 82 per cent. of all cases of Graves' disease and in 95 per cent. of those dying of heart failure following operation. In view of this, one is readily led to the surmise that a disorder of the thymus is an integral part of Graves' disease, and because of the similarity of some of the postoperative deaths to those of ordinary status thymico-lymphaticus, that the thymus may be responsible for some of the deaths. The thymus is reduced easily by irradiation, and it was, therefore, natural to try this in cases of exophthalmic goitre along with the treatment of the thyroid itself.

The effect of the X-rays, both on the thyroid and on the thymus in Graves' disease, is next to impossible to indentify pathologically. There is no experimental form of the disease and so we are dependent on its spontaneous occurrence in human beings. In the cases that improve, however, no tissue is obtained, and that from those which failed to improve and were subsequently operated on hardly forms a firm ground from which to draw inferences, for the very reason of that failure.

The ill effects on certain other structures, however, are easily discoverable and should be given due publicity so that they may be guarded against. First and foremost come the skin changes. If excessive or too prolonged dosage is employed, telangiectases, skin atrophy, and keratoses may develop, which later may become malignant; also laryngitis with or without necrosis of cartilage may occur.

"All of these conditions", says Holmes[11], "can be avoided by proper dosage. The group of skin changes are likely to occur if the dose is large enough to produce an erythema. Repeated treatments over a long period of time are somewhat more likely

to produce these changes than a single dose. They are likely to follow an erythema no matter how mild.

"Telangiectasis is the first to appear and is usually followed by skin atrophy and keratosis. Laryngitis is more likely to occur when heavy filtration is used or when the exposure is through more than one field, that is, cross-firing occurs. It can be avoided by using a single large field or by protecting the larynx with a lead covering. If the cartilage of the larynx is badly injured the results are apt to be serious." Vessel changes and skin atrophy were seen in some of our early cases. In women the disfigurement may be a serious matter. We are not getting these complications in cases treated at the present time.

Myxœdema[8, 12, 13] has been seen in several cases following X-ray, also after surgery. This will be discussed further later; at present, it may be said, that it is not a complication to be feared greatly. If it occurs it is readily treated with thyroid and often proves to be transient.

We have in the past published a number of histories of patients treated by X-ray[6, 7, 8, 14, 15, 16]. A couple more will be reported here to illustrate some of the points we have attempted to make.

Illustrative Cases

Case No. 1569. *Exophthalmic Goitre Responding Well to X-Ray Treatment*

History and Examination. — A married man of fifty-one, native of Vermont, and employed as an assistant railway supervisor, came under observation as an out-patient on July 10, 1922. He had all the classic symptoms of exophthalmic goitre, these having been present for a month. He was a large and powerfully built man with moderate exophthalmos and lid lag, slight symmetrical fullness of the thyroid with loud bruit, marked tremor, and sweaty skin. Basal metabolic rate on July 10, 1922,

was plus 74 per cent. and his pulse 109. It was clearly a case of moderately severe exophthalmic goitre for which no inciting cause could be elicited.

Management. — It was decided to treat him on an out-patient basis by X-ray, and he was also advised to keep as quiet as possible. He lived in the northern part of Vermont and was obliged to come to Boston for his treatments. This he was able to afford as he had a pass over the railway. The chart (Fig. 22) gives a good idea of his progress under X-ray therapy.

After a series of three exposures of two-thirds the erythema dose to thyroid and thymus areas, there was a very marked improvement. The goitre, eye signs, tremor, and tachycardia had disappeared on October 18, 1922, and there had been a satisfactory gain in weight. The patient had made four trips to Boston and had only incomplete rest; for a fortnight he had been back at work.

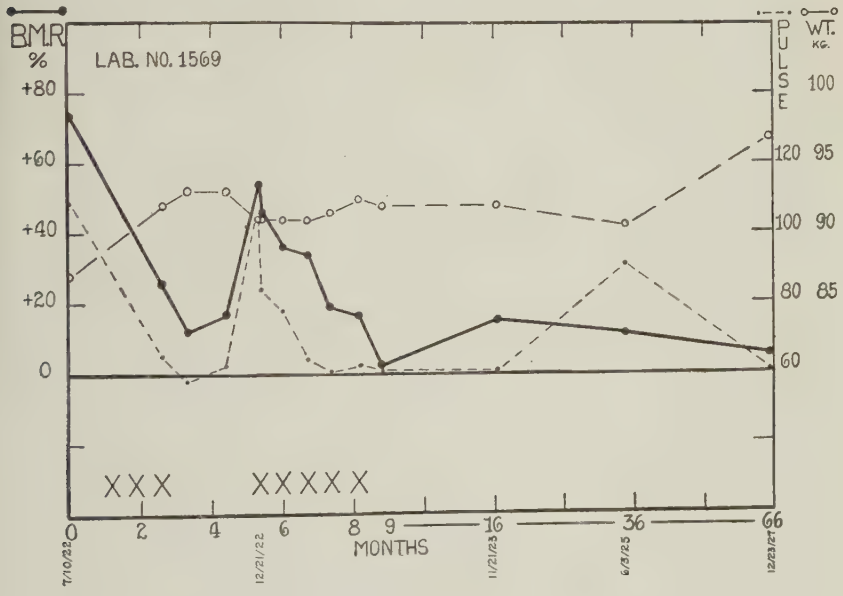

FIGURE 22. *Exophthalmic Goitre (Case No. 1569).* Response to X-ray treatment.

On December 20, 1922, however, he reported himself as being less well. The tremor, nervousness, fatigue, and excessive sweating had returned somewhat; the metabolism had risen to plus 55 per cent. He was clearly again thyrotoxic. A second course of X-ray was ordered and given as shown in the chart. Again there was very prompt improvement

both symptomatically and in the metabolism, although he stayed at work throughout.

When seen on November 21, 1923 he appeared to be cured. The same was true on June 3, 1925. He had remained at work and in good health. Nothing abnormal was found on examination at this time except a slight hypertension which probably had no relation to his past Graves' disease.

Comment. — There seems little reason to doubt that the improvement following each course of X-ray in this case was the result of the treatment. No other treatment was given, and there was practically no rest factor. To explain the results on the basis of coincidence is less convincing than attributing them to the treatment. Both the immediate and late results in this case compare very favorably with those obtained by surgery, and at no time during the program was the patient confined to bed, and during most of it he worked and earned his living. If X-ray could be depended upon invariably to work thus well, there would be little argument left on the side of surgery. Many cases, however, fail to respond in this manner.

Case No. 1510. *Exophthalmic Goitre: Apparent Cure by X-Ray Therapy; Subsequent Development of Hypometabolism*

History and Examination. — A single business woman of twenty-four, native of Massachusetts, came to the hospital for the first time on June 1, 1922 with a story of classic symptoms of exophthalmic goitre which had developed slowly a year before and which had become acutely aggravated three months before. She had had a goitre for two years. There was a moderate sized goitre and slight but definite eye signs, warm moist skin, rapid heart, and tremor. The basal metabolism was plus 47 per cent.

Management. — She was given one X-ray treatment in the usual way while in the hospital, and discharged to come back as an out-patient for the remainder of the treatments. Her progress can be inferred from the chart (Fig. 23). After three treatments she showed a marked improvement and returned to work. The metabolism dropped to a slightly subnormal level, and she gained considerable weight.

In March, 1923 the thyrotoxic symptoms recurred and the metabolism again rose, the pulse paralleling it closely. The weight again fell. X-ray treatments therefore were given with a second prompt symptomatic improvement in spite of the fact that she kept at work. Again the basal metabolic rate dropped below the average level and she gained

weight. She also noted that she needed to wear a sweater when her companions did not.

In August, 1923 she seemed in perfect health. The objective manifestations of Graves' disease were gone.

In January, 1926 she complained of chilliness and loss of strength. The basal metabolism was minus 14 per cent. She was started on a small dose of thyroid, 0.1 gm. ($1\frac{1}{2}$ gr.) (Armour's) per day. This relieved her symptoms and on April 13, 1926 it was increased to 0.2 gm. (3 gr.) per day.

In October, 1926, still on thyroid, she complained at the same time of nervousness, asthenia, and chilliness. It was thought that the eyes were again slightly prominent. On November 19, 1926 thyroid was omitted. The nervousness disappeared and the chilliness did not increase; her strength improved. In fact off thyroid she has remained well up to the time of writing (November, 1927).

Comment. — We believe that here, as in Case No. 1569, X-ray was responsible for suddenly altering the course of Graves' disease, precipi-

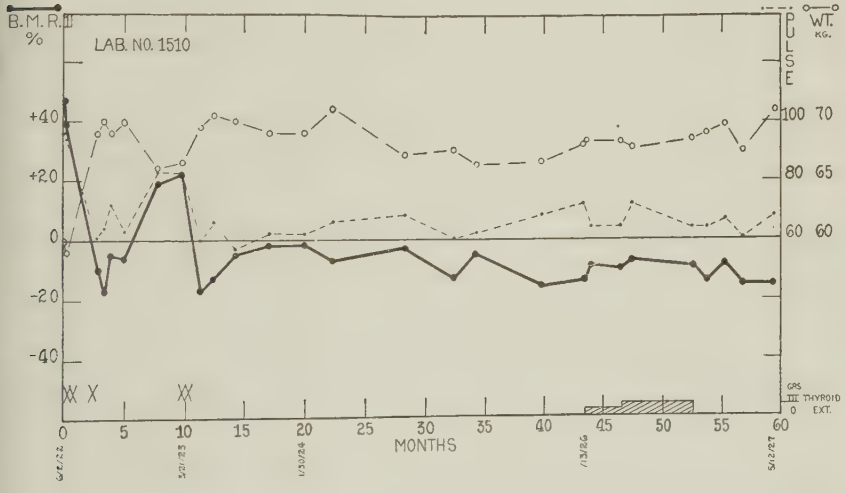

FIGURE 23. *Exophthalmic Goitre (Case No. 1510).* Apparent cure by X-ray with subsequent development of hypometabolism.

tating a remission, we may say. The subsequent fall to a slightly low metabolic rate is of interest particularly in view of the sort of experience we have since had in using iodine. In light of our more recent experience with iodine we would conclude that this patient's normal rate is really

below the average. She was not suffering from true myxœdema, but is rather to be regarded as a spontaneous low rate case. During the latter half of 1923, when her metabolism was within standard limits, she probably was suffering from mild hyperthyroidism. We would guess now that had iodine been given at that time, her basal metabolic rate would have dropped to the neighborhood of minus 20 per cent.

The development of hypometabolism, following the relief from thyrotoxicosis by whatever method it is attained, is of considerable practical interest. In the above case the phenomenon occurred twice in response to separate x-ray courses with coincident remissions.

This phenomenon occurred in approximately 20 per cent. of 200 cases in which the remission was produced by iodine preparation and subtotal thyroidectomy. It has also occurred in connection with prolonged medical treatment of cases under our observation (see case No. 15434).

A similar explanation could be entertained for the hypometabolism which developed in case No. 1432 reported on page 199 following x-ray treatment and bilateral ligation (q.v.). It also occurred in patients with menopausal thyrotoxicosis under medical treatment (No. 13754) and in the spontaneous course of the disease in the untreated patient. Hypometabolism in each of these instances seems linked with the tendency to remission which is so characteristic of the disease. This phenomenon has an interesting counterpart in the experimental animal, and the writings of Friedgood[66] should be consulted as throwing further light upon its significance.

Recently we have made use of this phenomenon in selecting patients for non-surgical regimes in the treatment of thyrotoxicosis and have found it helpful in several instances as a prognostic criterion.

Surgical Treatment

The chief factor, which has influenced the treatment of exophthalmic goitre, is the danger of postoperative toxic reaction. If patients having goitre with hyperthyroidism could have been operated on with as little risk as patients with simple goitre, the surgical treatment of this condition soon would have become firmly established. Early attempts at surgical removal, usually of one lobe only, met a prohibitive mortality from this cause. The problem thus became either to find some alternative form of treatment which was consistently effective, or to develop a reasonably safe method of surgical treatment. By means of careful preoperative preparation, followed in most instances by a series of operative procedures graded according to the patient's apparent resistance, preliminary ligation of vessels, thyroidectomy in one or two stages, perhaps with preparatory elevation of skin flaps, or delayed closure of the wound, leading up to eventual subtotal thyroidectomy, certain American clinics had an extraordinary success in the treatment of exophthalmic goitre. The actual mortality was very difficult to determine, partly because death percentages were figured in relation to operations which might be multiple rather than in relation to patients, and partly because some operative figures were diluted with non-toxic goitres carrying a low risk. It was probably not far from 3.5 per cent., which was a very satisfactory figure considering the serious results of the disease. But if these satisfactory results were true of a few clinics, they were not true of hospitals receiving relatively few cases of the disease, in which the mortality can only be conjectured, and certainly not true of our own hospital. On this account, the effect of X-ray therapy was followed carefully, as we described in the previous section.

The postoperative toxic reaction is of sufficient importance, therefore, to merit description before discussing further the surgical treatment. Essentially it consists of an intensification of symptoms and resembles the occasional crises occurring spontaneously during the course of the disease, more common in the interior of this country than on the Eastern seaboard, which cause a considerable part of its natural mortality. In typical cases, the patient goes through operation satisfactorily, although perhaps with a very rapid pulse and progressive fall in blood pressure. After reaching bed, he may show a decrease in pulse rate and appear in good condition, although he may complain of an indescribable sense of oppression. This interval may last six or eight hours, following which the pulse rate increases, the temperature rises, and the nervousness becomes intensified. The fever may go to 105° or 106° F. the pulse to 180, 200, or even higher; the patient tosses about in uncontrollable restlessness, is excitable, talkative, apprehensive, and perhaps delirious. Vomiting is likely to be persistent. The reaction reaches its maximum at the end of about thirty hours. Coma may follow the acute nervousness, in which death takes place with an uncountable pulse and a hyperpyrexia of 107° or 108° F. If the patient survives the period of greatest intensity, a steady improvement usually occurs. This picture naturally presents variations. Death may take place directly after the operation or within an interval of a few hours. The toxic state brings about a susceptibility to pulmonary infections. These fatal cases were of course exceptional. It was common, however, to see a well marked reaction following operation, with increased restlessness, rapid pulse, vomiting, and fever, the degree of which provided the best single guide to the intensity of the condition.

The cause of this reaction remains unexplained. It has been attributed to absorption from the wound surfaces or to an excessive discharge of thyroid secretion incidental to the operative manipulations, and even by one writer to precisely the reverse[17]. The reaction may occur after operations outside of the thyroid area. A typical reaction caused death in a patient with exophthalmic goitre after cholecystectomy for a gangrenous and perforated gallbladder. Holman[18] in one case found hypoglycæmia associated with a severe postoperative reaction which responded well to the administration of glucose. In a series of cases observed following operation in this clinic[19], no evidence of hypoglycæmia occurred, but we have had no occasion to follow the blood sugar during a severe reaction. It is reasonable to suppose that the increased metabolism following operation, shown by Segall and Means[20] to reach a maximum after about twenty-four hours, the restlessness, pyrexia, and starvation should make excessive demands on stored carbohydrates. Whatever the cause, this reaction makes it impossible to judge by ordinary standards the resistance of a patient with hyperthyroidism to operation. A similar lack of tolerance to operative procedures in patients, who otherwise appear fair risks, is difficult to find in surgery. It occurs in status thymicolymphaticus, but without the conspicuous symptomatology.

The patients, who were liable to a severe reaction, were difficult to separate except in a general way. It could be said that those cases with advancing toxæmia and progressive weight loss, those with high metabolism, and those with nervous fear of operation were bad risks from this cause. But these cases did not include all who were liable. On this account it was customary to resort to graded operations in all cases except those who showed clearly by the mildness of their disease, by the tend-

ency to improvement, and by the absence of visceral damage, that they were good risks.

Measures to avoid this reaction did not extend beyond rest in bed, a high caloric diet, the treatment of complicating factors, and efforts to gain the confidence of the patient and to diminish the excitement incident to undergoing a dreaded operation. This last was sometimes accomplished through group psychology by means of contact with patients who were successfully convalescing, or, as in the Crile[21] clinic, by concealing the actual occurrence of the operation from the patient.

Operation in successive stages, therefore, was the means chiefly depended upon before the introduction of iodine to secure subtotal removal of the thyroid without precipitating a serious postoperative reaction. While patients benefitted by X-ray treatment were to that extent rendered better risks for operation, we were unable to show that those without improvement were less liable to a reaction on account of the effect of radiation on the thymus[22]. X-ray treatment, as carried out in our clinic, did not increase the technical difficulties of the operation.

The use of graded operations, although necessary for the safety of the patient, carried with it certain obvious disadvantages. The chief of these was the time required in some cases to secure an adequate removal of the thyroid. In a severely toxic case the procedure would be somewhat as follows. The superior thyroid vessels would be ligated on one side under local anæsthesia. From four to ten days later, according to the degree of reaction, the superior thyroid vessels on the other side would be tied. After convalescing, the patient would be discharged under observation, to return in six weeks to two months for thyroidectomy. At this second entry, the extent of operation would be decided by the patient's general condition and his

tolerance during its performance. If there was any question as to his ability to survive a subtotal removal, operation would be limited to hemithyroidectomy, and the patient again discharged, to reënter after another two months for excision of the remaining lobe. Thus four months might elapse before the full therapeutic effect of surgery was obtained. If a previous course of X-ray treatment had been given unsuccessfully, relief of toxæmia might not be secured for seven months or more. In some instances the time required for completing the surgical program might be shortened by performing a double superior ligation as one step, or by carrying out a hemithyroidectomy as the first stage of the procedure. A minority of patients only underwent immediate subtotal thyroidectomy. This system had obvious disadvantages for the patient, in the expense, the time required, and the mental suffering and physical discomfort incident to repeated operations. Under these conditions, the X-ray, if reasonably effective, might be a real competitor with surgery.

CASE NO. 1771.—*Exophthalmic Goitre: Old Style Operative Program*

History and Examination. — A housewife of 54, born in Cork, Ireland, was first admitted to the hospital on November 27, 1922. At that time the cardinal manifestations of Graves' disease were all present. The history, however, was somewhat unusual. Fifteen years before entry her family noticed enlargement of the thyroid, but there were no general symptoms. Ten years ago her eyes became prominent, but there were no further symptoms until a year ago when a progressive weight loss was noticed. Six months ago she began to have distress on exertion, with a rapid pulse even at rest. During the last three months she had had attacks of persistent vomiting with headache. She had lost forty pounds in the last six months. Examination showed an emaciated woman with mild congestive heart failure. The thyroid was small. X-ray of chest was negative for substernal goitre.

Management. — Operation was considered particularly desirable on

account of the cardiac involvement. After two weeks rest in bed she improved somewhat, and her metabolic rate dropped from plus 48 per cent. to plus 37 per cent. and her pulse from 130 to 120. In spite of the relatively slight elevation of metabolism, she was thought to be a bad operative risk on account of her emaciation and recent intensification of symptoms. Consequently a program of graded operations was decided on. The right superior vessels were ligated under local anesthesia on December 9th and the left on December 18th. There was very little reaction to these operations and she was discharged on December 24th.

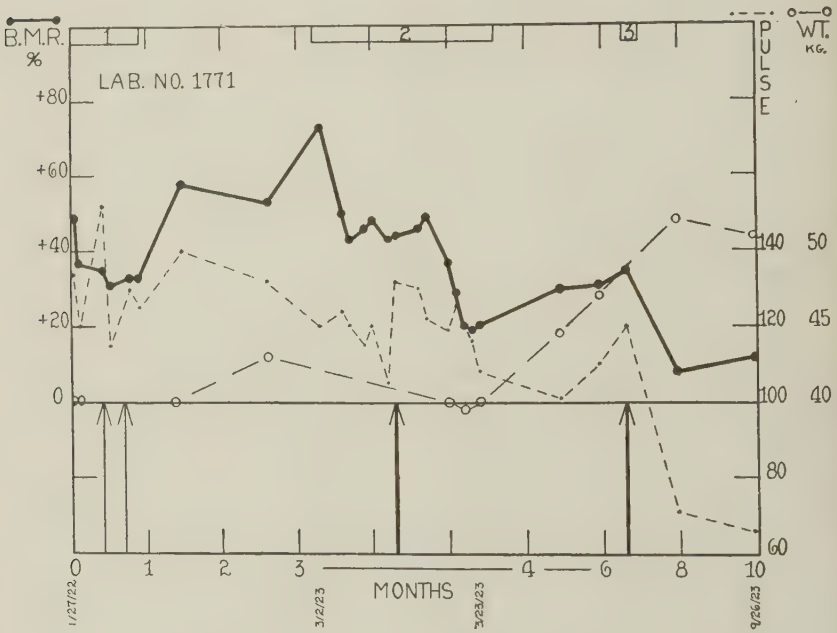

FIGURE 24. *Exophthalmic Goitre (Case No. 1771).* Old style operative program.

She returned to the hospital on March 1st and stated that she was stronger and less nervous. No effect of ligation upon pulse or metabolism could be shown, but she had gained 3 kilos. Operation was postponed for ten days to secure complete digitalization. At operation five-sixths of the right lobe of the thyroid was removed under gas-oxygen anæsthesia. Operation was ended at this point on account of the rapid pulse rate. She had a moderately severe postoperative reaction, with a pulse above 140 for three days. She was discharged on the thirteenth day. The tissue removed weighed 15 grams and showed follicular hyperplasia of the type associated with Graves' disease.

This operation was followed by a definite gain in weight and improvement in general condition. She became able to do her own housework but her metabolic rate and pulse rate were not much affected. She was sent into the hospital for completion of the surgical program. She had gained 8 kilos.

On June 13th a similar removal of the left lobe was carried out, which was much better tolerated. She was discharged 9 days later. Examination of the vocal cords showed no paralysis.

On July 25, 1923, she showed remarkable improvement both mentally and physically.

A year later, July 13, 1924, her improvement had been maintained. Her right eye was normal, but some exophthalmos persisted in the left. There was no evidence of hyperthyroidism, and the patient was able to do her regular work.

Comment. — This patient shows a type of disease not infrequent beyond middle life. Apparently she had a mild type of Graves' disease for many years, which was well tolerated, and then suddenly for no known reason, an acute exacerbation. A clinical course of this type is somewhat suggestive of adenomatous goitre with hyperthyroidism, but the pathologic changes in the thyroid were characteristic of exophthalmic goitre. On account of the rapid weight loss, with vomiting, the situation required careful handling. In determining the extent of operation we considered principally this factor together with the general condition of the patient, rather than the metabolic observation. It was not worth while to jeopardize the patient by finishing the operation at the second stage. After completion of the operative program, the patient's gain in general health was very satisfactory, but it required a subtotal, rather than a hemithyroidectomy, to accomplish the result.

Case No. 2995. *Exophthalmic Goitre: New Style One-Stage Thyroidectomy in Iodine Remission*

History and Examination. — An American housewife of 24 entered the hospital on January 27, 1925, with all the cardinal signs of exophthalmic goitre except that the exophthalmos was slight. She gave a story of slight enlargement of the thyroid for four years, accompanied by increased appetite and loss of weight. During the past six months the symptoms had become progressively worse. When first seen she had a metabolic rate of plus 80 per cent., but she was considered a case of moderate severity without complications.

Management. — She was put to bed on a liberal diet with plenty of

fluid. On the third day Lugol's solution, m. 30 (2 cc.) per day was started (m. 10 t.i.d.). On this the symptoms and signs receded. Her basal metabolic rate which was plus 68 per cent. when the iodine was begun dropped 40 points; her pulse dropped from 108 to 74, and she gained 1.5 kilos. She received no other medication. Examination of the larynx showed that the vocal cords moved freely and approximation was perfect. An X-ray was negative for substernal goitre and showed a few calcified glands, while the apices and periphery of the lungs appeared clear.

Preparation for operation disturbed her routine as little as possible. No fluids were given after midnight. She received a suds enema in the morning, and morphia gr. $\frac{1}{6}$ (10 mgm.) an hour and a half before operation, which was repeated with atropine gr. $\frac{1}{120}$ (0.5 mgm.) one hour later. Anæsthesia was by gas-oxygen, which went satisfactorily. The field of operation was prepared with tincture of iodine. The operation was done through a collar incision; in this instance, on account of the moderate size of the goitre, the muscles were separated in the median line instead of being divided. The thyroid was mobilized by ligating the superior thyroid vessels and the middle thyroid veins. Both lobes of the gland were removed leaving only their posterior portions over the recurrent nerves and trachea. The tissue remaining was estimated to be one tenth of the gland. Hæmostasis was secured, and the muscles sutured in the middle line. The skin was closed with clips. Two rubber drains were inserted to the thyroid bed. The postoperative reaction was moderate, the pulse reaching 120 and the temperature 102° F. on the second day. On the patient's return to the ward icebags were applied to the neck, precordia, and axillae. She was given rectal injections of water and 5 per cent. glucose solution alternating at four hour intervals. With the water was given Lugol's solution m. 15 (1 cc.). She received morphia gr. $\frac{1}{6}$ (10 mgm.) three times on the day of operation and on the following day. The wicks were removed on the second and the skin clips on the fourth day. On the second day rectal fluids were omitted, Lugol's solution m. 10 (0.6 cc.) t.i.d. was given by mouth. The patient was taking liquids and soft solids freely. Convalescence was uneventful. She was discharged on the twelfth day, directed to take five minims of saturated solution of potassium iodide every other day. The larynx was normal. There was still some slight serous discharge from the wound. The progress is indicated by the following chart (Fig. 25).

On April 7, 1925, she reported after a severe attack of tonsillitis two weeks previously. Weakness was the only complaint, with some dyspnœa on exertion. The exophthalmos had receded entirely. The tremor had disappeared. The wound was still indurated. Her basal metabolic rate was minus 3 per cent., and she had gained 3 kilos. She was advised to continue potassium iodide and to diet so as not to gain more weight.

On June 7, 1925 she had no complaints, there were no toxic signs or symptoms and the scar was very good. She was advised to stop iodine.

September 5, 1925 she felt quite well, except for a slight residual nervousness which was gradually improving. Her basal metabolic rate showed no variation from standard and she had lost a little weight.

On January 7, 1927 she reported that a $7\frac{1}{2}$ pound son, her first child, was born on August 31, 1926, after a difficult labor. She felt well but had little energy, and tired rather easily. She was inclined to brood over

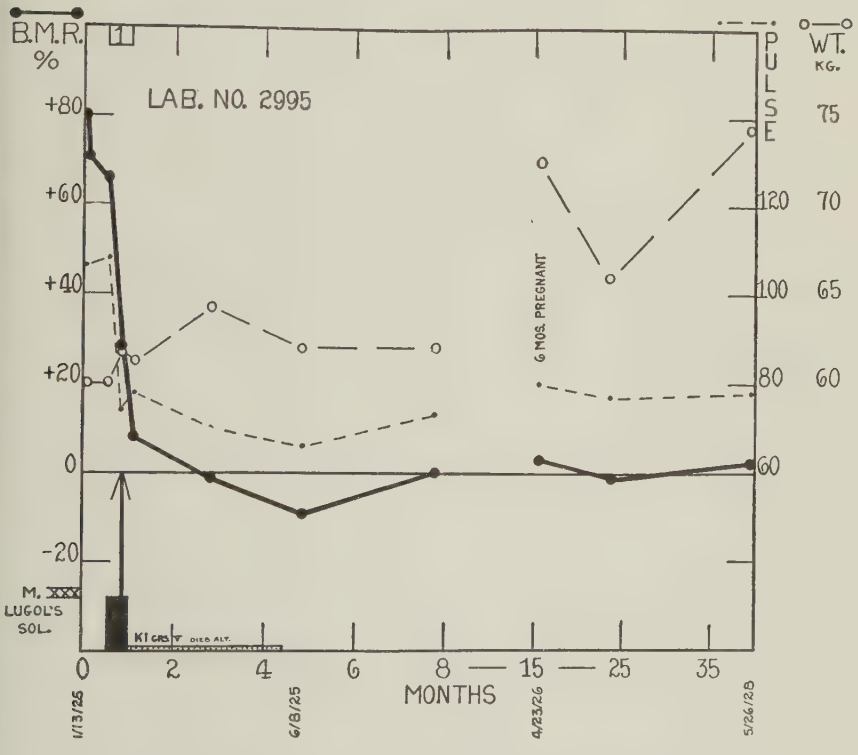

FIGURE 25. *Exophthalmic Goitre (Case No. 2995).* New style operative program. One stage subtotal thyroidectomy in iodine remission.

little things and cried easily, although she slept well. There was no tremor, no palpable thyroid, and no dryness of skin or hair. Her metabolic rate was minus 1 per cent. She was advised to continue her usual life without the use of iodine.

Comment. — This case illustrates well the modern program of one-

stage subtotal thyroidectomy in a full iodine remission. Everything went well up to and through the operation. Her condition since has been satisfactory, particularly with regard to restoration to a normal metabolic plane and the tendency to gain weight. Here, as not infrequently happens, a restriction of diet became advisable. Nevertheless there was a slight residuum of fatigableness and nervousness, which may be peculiar to the individual, but which occurs so frequently as to be more probably attributable to the disease. The patient went successfully through pregnancy and a difficult labor without return of hyperthyroidism.

CASE NO. 1432. *Exophthalmic Goitre: Irradiation without Relief Followed by Ligation of Arteries with Nearly Complete Relief*

History and Examination. — An American housewife of 22 entered the hospital May 20, 1922, having had symptoms consistent with Graves' disease for one year, and presenting the cardinal objective signs. The impression was that the case was one of moderate severity. No complicating factors were discovered.

Management. — After eighteen days' rest in bed there was slight improvement. X-ray therapy was decided upon to be given on an outpatient basis. Accordingly she was discharged and a total of five X-ray treatments were given subsequently as shown in the accompanying chart (Fig. 26).

These were productive of no striking improvement and therefore on October 3, 1922, she was readmitted to the hospital, this time for operation. On October 9, 1922 a right superior polar ligation was done under gas and oxygen and on October 17, 1922, this same procedure under the same anæsthetic was done on the left. From these she made a satisfactory improvement and was discharged on October 22, 1922.

She has been followed since with observations of the metabolism over a period of nearly five years. On the whole, she has been well. The symptoms of Graves' disease were practically gone by December 14, 1922.

In the Autumn of 1923 there was a low basal metabolic rate, and this was still present but in lesser degree three years later. There never were any hypothyroid symptoms beyond slight dryness of skin and hair. She also complained at times of some asthenia. Lugol's solution and then thyroid were tried for the residua without any noteworthy effect except on the basal metabolic rate. The symptoms without medication did not amount to enough to preclude the statement that she was essentially cured.

Comment. — This case is presented as a curiosity rather than a type.

Following what seemed to be a failure with X-ray a rapid and extraordinarily good result with ligation alone occurred. It had been intended of course to proceed with the surgical program through thyroidectomy, in more than one stage if necessary. The remarkable and unexpected improvement after ligation, however, which later proved permanent, made thyroidectomy unnecessary.

We have no other case that has behaved quite in this way. It is offered, therefore, as an interesting exception to what usually happens, rather than as a routine method of treating exophthalmic goitre. The

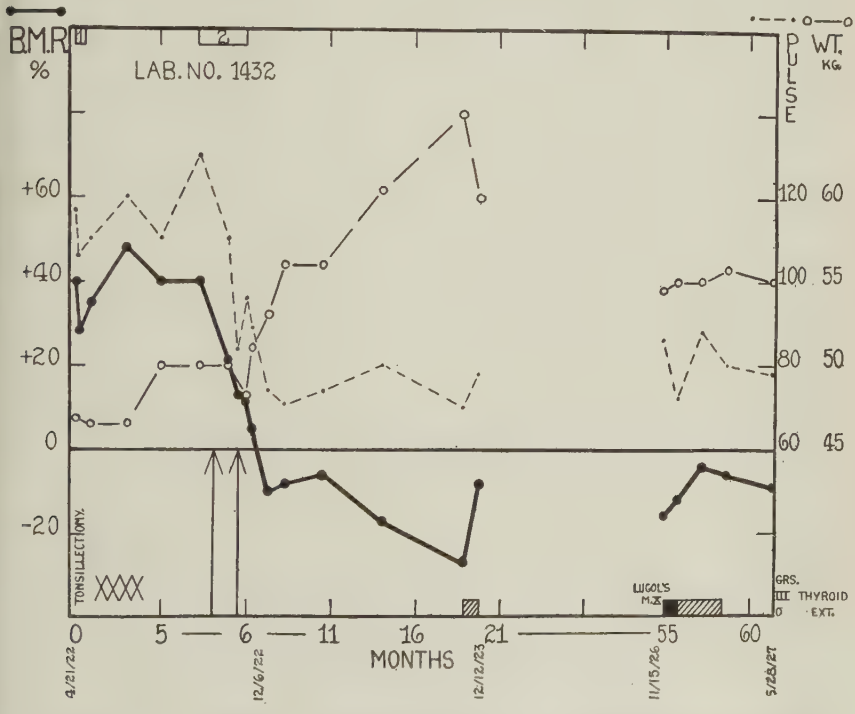

FIGURE 26. *Exophthalmic Goitre (Case No. 1432).* X-ray treatment without relief followed by ligation of arteries with nearly complete relief.

significance of the subsequent low metabolism is not clear. It seems in this case not to be of a permanent variety.

In the course of observation of patients undergoing these successive operations, data have been secured as to the effect of these various procedures, at least for a non-goitrous district.

Locality, as we pointed out earlier, plays an important part in determining the type, course and reaction of the disease. Plummer[23], for instance, finds the mortality in exophthalmic goitre distinctly higher in cases originating west of mid-Indiana than in those east of it and believes geography more important in determining operative mortality than the details of operative technique..

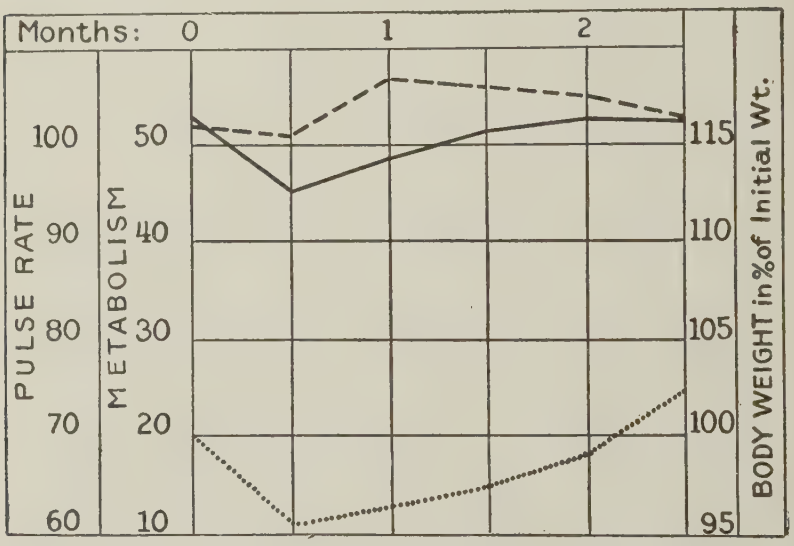

FIGURE 27. *Exophthalmic Goitre.* Effect of ligation of superior arteries. Composite chart of 11 cases in which X-ray treatment had not been used previously. Solid line, basal metabolism; interrupted line, pulse; dotted line, weight. The curves begin at the time of the operative procedure. (After Richardson and Means.)

Ligation of arteries, in our clinic limited to the superior vessels, habitually has included the vascular bundle entering the superior pole, and consequently any effect produced may have been due to nerve injury or to occlusion of lymphatics or veins rather than to interference with arterial circulation, which is admittedly slight on account of the rich anastomosis. It was always planned as a preliminary to thyroidectomy, but never-

theless, on account of unexpected improvement, it remained the sole form of treatment in three cases.

That ligation reduces the risk of subsequent thyroidectomy has been believed generally by surgeons. This is a difficult point to prove statistically. Our own data are not extensive enough to warrant a statistical conclusion. Certainly the improvement judged clinically is not very striking. Richardson and Means[22] were able to observe the immediate effect of the operation upon metabolism, pulse and weight in a series of eleven patients who had had no previous X-ray treatment and in

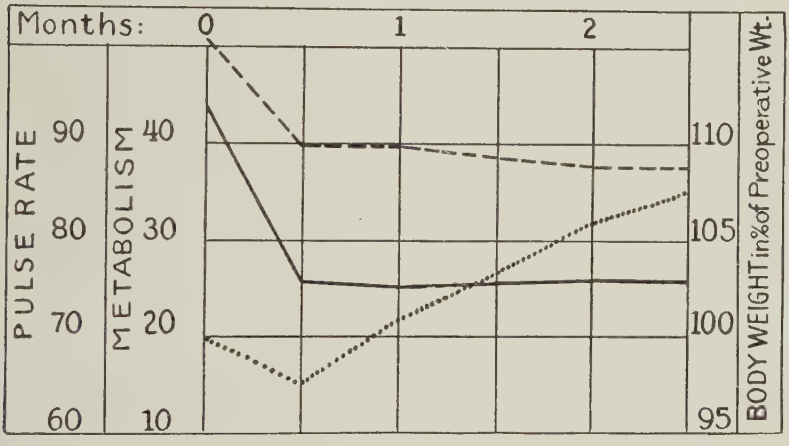

FIGURE 28. *Exophthalmic Goitre.* Effect of ligation of superior arteries. Composite chart of 7 cases treated previously by X-ray. Solid line, basal metabolism; interrupted line, pulse; dotted line, weight. The curves begin at the time of the operative procedure. (After Richardson and Means.)

a series of seven who had been irradiated. The composite curves showing the course for two months after operation will be found in Figs. 27 and 28. In both groups the effect on the pulse rate is nil, and in the first that on metabolism likewise. The second group shows a slight fall in metabolism. In both there is first a loss of weight, then a gain, but aside

from that, taken all in all, the evidence of real benefit, clinical or laboratory, judged from this extremely small series of cases is slight. However, this is far from telling the whole story. In the first place, ligation is an extremely valuable procedure for testing the patient's reaction to operation, and consequently of his ability to go through a more extensive procedure. It also gives the patient increased confidence as well as familiarity with hospital and operating room conditions. Finally, thyroidectomy, if postponed for two months, usually is undertaken at a period when the patient is gaining weight. Relatively few deaths from toxæmia occurred after thyroidectomy in patients who underwent preliminary ligations. On looking back on this period we regret that ligation was not done more often. At present the benefit obtained from preparation of the patient with iodine is so striking that resort to ligation is unnecessary in the great majority of cases. Nevertheless, it is well to retain it as a test procedure in seriously toxic patients who are refractory to this drug.

Hemithyroidectomy, or possibly removal of one lobe together with the isthmus of the thyroid, was for many years the extent of operation commonly advised in exophthalmic goitre. This operation is naturally less extensive than subtotal thyroidectomy and consequently should carry less operative risk, so that it was frequently used as a step in securing subtotal removal. While this procedure led to clinical improvement, too much thyroid tissue remained to secure complete relief of symptoms, at least as an immediate effect. The late results were often surprisingly good. Thus in 1923, C. A. Porter[24], in analyzing the end results of thyroid surgery in cases done by him at the Massachusetts General Hospital and privately, found the average metabolism in thirty-two cases in which hemithyroidectomy had been done

three or more years before to be plus 4 per cent. The immediate effect, however, is not a complete restoration to a symptom-free state and normal metabolic level. Richardson and Means[22], for example, studying intensively the early results in twenty-three cases, found as shown in Figs. 29 and 30 that pulse and metabolism, as indicated by composite group curves, in the first two weeks drop about half way toward normal and then remain essentially stationary for two or more months. The

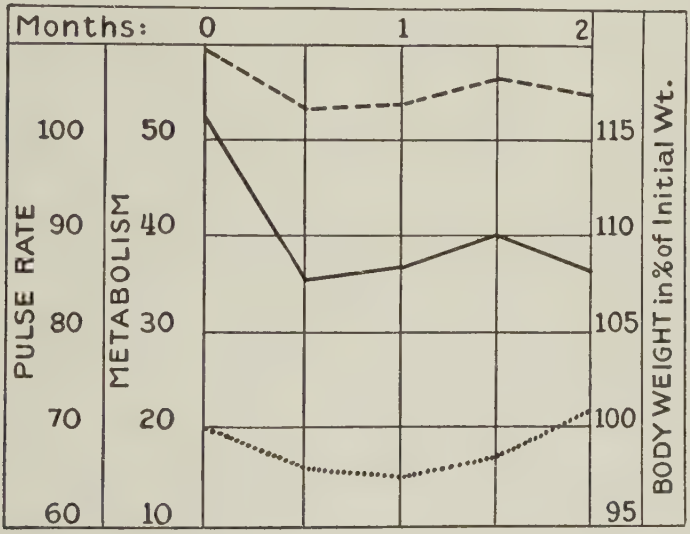

FIGURE 29. *Exophthalmic Goitre.* Effect of hemithyroidectomy. Composite chart of 13 cases not treated previously by X-ray. Solid line, basal metabolism; interrupted line, pulse; dotted line, weight. (After Richardson and Means.)

weight, however, after the second week shows a steady gain. The cases are divided into those which had not had previous treatment and those which had been irradiated. There was nothing about the latter group as a whole to indicate that previous X-ray had enhanced the benefit from surgery.

Our conclusions regarding hemithyroidectomy finally were that it is an incomplete procedure. It makes patients with

Graves' disease better, but it does not make them well. Often for many months after operation they remain toxic, though less so than before. By comparison with their previous state, however, their condition subjectively may seem satisfactory, and finally after a year or two the disease, having run its course in modified form, leaves them to all intents and purposes well. Of course in many of our cases a first partial thyroidectomy was followed by a second, and a total result amounting to the present day so-called subtotal thyroidectomy was achieved. In these, after the second operation, as in one stage subtotal

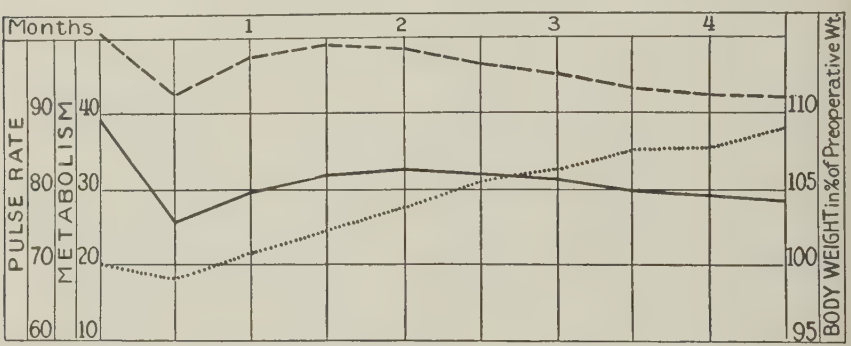

FIGURE 30. *Exophthalmic Goitre.* Effect of hemithyroidectomy. Composite chart of 10 cases previously treated by X-ray. Solid line, basal metabolism; interrupted line, pulse; dotted line, weight. (After Richardson and Means.)

thyroidectomy, the patient usually was rendered symptom-free and restored promptly and permanently to a normal metabolic plane, but the single hemithyroidectomy was for the most part a palliative rather than a curative procedure. It began a cure which nature in time often completed.

It should be mentioned also that in not a few cases after hemithyroidectomy a considerable increase in size occurred in the remaining lobe along with increase in the symptoms of hyperthyroidism. Under these circumstances a second operation

practically always was advocated, and if refused, X-ray treatment employed instead.

Subtotal thyroidectomy. — The ablation of five-sixths or more of the thyroid brings about in many instances a complete and prompt relief of symptoms, together with restoration to a normal metabolic plane. Certain striking exceptions, however, will be discussed under sequellæ. The proportion of gland remaining varies with each case. In general, cases with severe toxæmia and high metabolism require more complete removal of the gland than mild cases if a normal metabolic level is to be secured. The surgeon is between the devil and the deep sea. If too little thyroid tissue is removed, the symptoms are not relieved completely and the metabolic rate remains elevated indefinitely. If the removal is too extensive, there is greater danger of interfering with the parathyroid glands, and possibly with the recurrent nerves. In general, the best interests of the patient are served by as complete a removal as seems safe, since not only is persistent toxæmia avoided, but the patient who has had exophthalmic goitre is better off with a subnormal metabolism.

The precise effect of subtotal thyroidectomy has been studied intensively in our clinic. In 1924 Segall and Means[20] reported a series of daily observations of the metabolism, pulse and temperature in fourteen cases in which either a subtotal thyroidectomy or a secondary operation which completed a removal of gland substance amounting to a subtotal thyroidectomy was done. None of these had iodine. Three of these cases were considered adenomatous rather than exophthalmic goitre. The composites of the metabolism, pulse and temperature curves of eleven of the cases which averaged between plus 40 per cent. and 50 per cent. for metabolic rate before operation are shown in Fig. 31. It will be noted that they were fairly in equilibrium

before operation so that it is safe to attribute the subsequent happenings directly and entirely to that procedure. The day following operation there is a sharp peak in all curves but thereafter a steady fall reaching normal about the eighth day. Just what determines the rate of drop it is impossible to say. Were the thyroid completely removed, each point in the curve

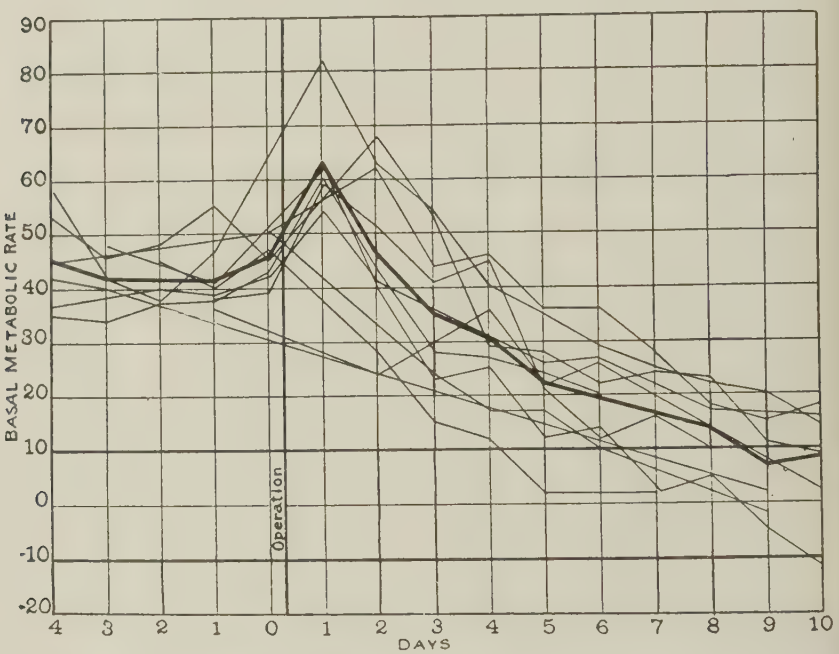

FIGURE 31. *Toxic Goitre.* Effect of subtotal thyroidectomy. Basal metabolism curves in 11 cases of exophthalmic and 3 cases of adenomatous goitre. The heavy line represents the composite. (After Segall and Means.)

would denote the quantity of thyroxin remaining in the body and its slope the rate of destruction or loss of this hormone Under these circumstances, however, the curve would not flatten out at the normal level but would continue to fall to the level of complete myxœdema. The fact that the curve flattens out at the normal level shows that the remnant of thyroid left

is capable of supplying an essentially normal quantity of thyroxin. When one considers how physiologically crude a procedure removal of five-sixths of a hyperplastic gland is, it must be regarded as truly remarkable that so perfect a restitution to a normal functional status can be obtained. In Fig. 32 the operative curves are compared with the Lugol's solution curves discussed in the previous chapter. Except for the peak on the day following operation, the two are nearly superimposable,

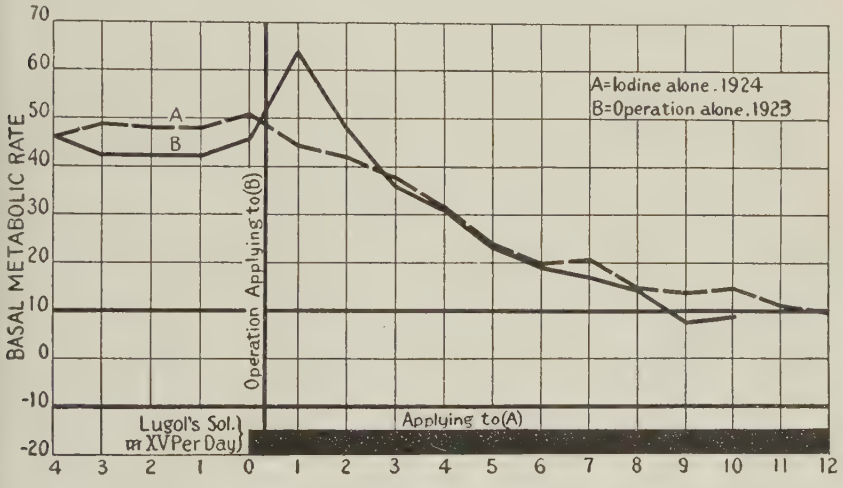

FIGURE 32. *Exophthalmic Goitre.* Effect of iodine as compared with that of subtotal thyroidectomy without previous iodine treatment. The composite curves are from Figs. 14 and 31. (After Starr, Segall and Means.)

which indicates that whatever Lugol's solution does, it is equivalent metabolically for the time being to the ablation of five-sixths of the thyroid.

The slightly later effects of subtotal thyroidectomy are shown in a series of twenty cases reported by Richardson and Means[22] (Fig. 33). The most important points brought out by this chart are that pulse and metabolism are restored to normal within two weeks and remain flat through the fourth month,

while body weight shows a steady gain during this period. Often this gain is sufficient to produce actual obesity, and Thompson[25] has called attention to a certain puffiness and placidity of the face which is often quite striking in the early months after operation and in marked contrast to the thin and anxious expression of preoperative days.

In contrast to hemithyroidectomy, therefore, subtotal thy-

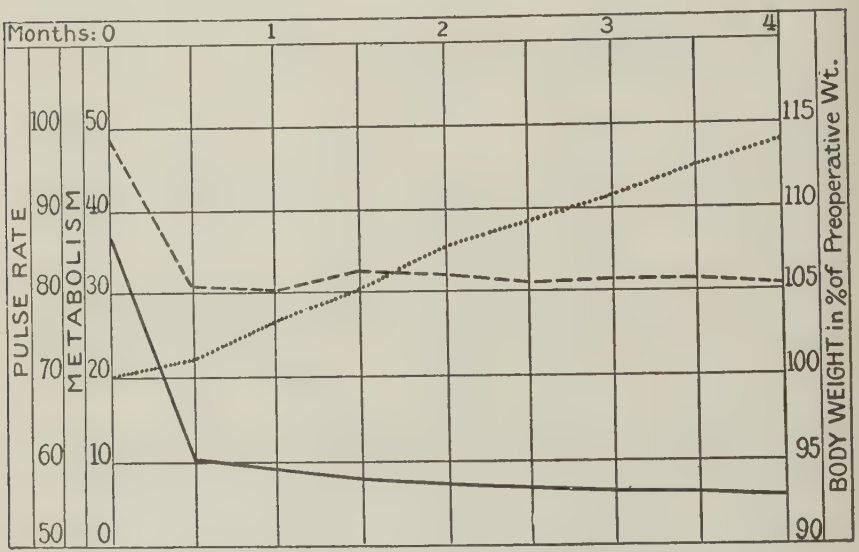

FIGURE 33. *Exophthalmic Goitre.* Later effect of subtotal thyroidectomy without previous iodine treatment. Composite chart of 20 cases. Solid line, basal metabolism; interrupted line, pulse; dotted line, weight. The curves begin at the time of the operative procedure. (After Richardson and Means.)

roidectomy is usually a curative procedure. Not only is the individual restored promptly to an essentially normal status, but in most instances this is permanent. A few typical cases will be cited presently. In passing we might note that certain surgeons have even advocated total thyroidectomy in exophthalmic goitre, with later thyroid administration to control the

resulting myxœdema[26]. The desirability of such a radical procedure is open to very serious question, and it seems to us unlikely that it will ever come into general use.

Rôle of Iodine in the Treatment of Exophthalmic Goitre

Having discussed the two types of procedure, irradiation and surgical resection, which seek to diminish the functional activity of the thyroid, we feel that it is now appropriate to take up the rôle of iodine in relation to these. The peculiarities and significance of the iodine remission have been discussed in a previous chapter. We are now concerned with the use that can be made of this reaction in getting the patient well.

In the first place it may be proper to point out that in the days previous to iodine we had reached the point of advocating X-ray in most cases first and operating in those that did not then do well. This was obviously because X-ray was not dangerous and might effect a cure, whereas surgery, though giving brilliant results, in many instances carried an appreciable mortality. From the beginning of 1920, when our thyroid clinic was established, through 1923 the mortality was 7 per cent. Most of the deaths in this period were due directly or indirectly to postoperative toxæmia. Routine preparation with iodine was begun in June, 1923. From 1924 to 1927 inclusive, the mortality was 2.4 per cent. Of four deaths occurring during the latter period, none was from acute thyrotoxicosis. These figures, it should be remembered, are for a general hospital serving the poorer classes of the population and are not directly comparable with private clinics specializing in thyroid disease. Nevertheless, they serve to show the striking effect produced by the introduction of iodine as a preparatory measure.

Reduction of the need for preliminary operation is another

beneficial result of preoperative treatment with iodine. Thus the percentage of complete operations in one stage (immediate subtotal thyroidectomy) has risen from 29 per cent. to 92 per cent., and in spite of this increased proportion of radical operations, the incidence of postoperative reaction has diminished greatly. Clute[27], similarly, has reported 38 per cent. of one stage operations in the days before use of iodine and 63.7 per cent. since. He also reports pole ligation as being done in 51 per cent. of the cases before iodine was used, in 13 per cent. since. In our own clinic ligation has been done but twice since the use of Lugol's solution was introduced.

One striking effect of iodine is shown by the patients' mental state after operation. Instead of being toxic, emotional and restless, they are ordinarily quiet, and as readily controlled by morphia as the average postoperative patient. While no alarming instance of acute thyrotoxicosis has developed, postoperative toxic reactions of moderate severity still occur occasionally. It is too much to say that fatal toxic crises have been abolished by preliminary treatment with iodine, although we have had none since iodine was introduced. Each case should be judged upon its merits, and if for any reason a patient appears to be a particularly bad risk because of toxæmia, a limited operation should be performed. In forming this judgment one ought to see the patient before iodine has been given; otherwise the degree of improvement may be so great that a false impression of security may be got. As to the reason why iodine should reduce the postoperative reaction, we are as much at a loss as we are in knowing what produces the reaction in the first place. This effect is due to something more than the general physical and mental improvement brought about by the use of the drug; the quality of the patient's tolerance of anæsthesia

and operation is changed. Consequently the important fact is that the patient should be saturated with iodine before operation; the actual remission secured as shown by the drop in metabolism and pulse rate is of less importance, and can not be taken as an index of the patient's resistance to the effect of operation.

Surgery in the past, therefore, not only carried risks of an impressive sort, but also to be relatively safe required in most cases a time-consuming and trying ordeal of repeated operations. Now, thanks to the use of iodine to abolish the so-called crisis status, as suggested by Plummer, all is changed. We are prepared to agree unequivocally that iodine so used practically precludes operative deaths from thyrotoxicosis, the cause, either directly or indirectly, of most of the deaths occurring previous to 1923.

Authors' Conception of the Best Treatment

The best treatment at present for exophthalmic goitre, according to the unanimous opinion of the staff of our clinic, is subtotal thyroidectomy in an iodine remission. Similar views are expressed by many other writers[28, 29, 30, 31, 32, 33]. It was always granted that adequate resection, if it did not kill, brought about a quicker cure than anything else. Now if iodine nearly wipes out the risk, and particularly if it makes a single and sufficiently extensive one stage operation possible, thus abolishing the trying piecemeal program of earlier days, there is little that can be said in favor of any other program. We have been accused of changing our minds regarding X-ray. In point of fact we have done nothing of the sort; we have merely admitted that something better has come along and are looking and hoping for something better still. If we had had exophthalmic goitre ourselves in 1922, we should have wanted a trial of X-ray treatment

before any operation was done. If we had it now, we should want iodine at once and a subtotal thyroidectomy as soon as our pulse and metabolism had approached normal, in ten days more or less.

The actual routine at the Massachusetts General Hospital at present is as follows. Patients are advised to enter the hospital directly the diagnosis is made. They put are to bed and Lugol's solution in doses anywhere from 0.6 to 3 c.c. (10 to 45 minims) per day is begun. There is no fixed rule about the dosage. It is possible that much smaller ones than those usually employed would serve[34]. A study of iodine dosage is now in progress in our clinic. In general the very toxic cases get 3 c.c. (45 minims), the moderately toxic 2 c.c. (30 minims), and the mild 1 c.c. (15 minims) a day of Lugol's solution. If they did not show the desired improvement on 3 c.c. (45 minims) we should go higher, but in Boston this is rarely necessary. In goitrous districts it may be so more frequently.

The necessity of rest in bed is debatable. For the very sick patients undoubtedly it is necessary. Others might get satisfactory remissions on an ambulatory basis. Dr. Plummer does this at Rochester. Since rest alone brings about some improvement, we have believed that it should be included as part of the preoperative program. The amelioration of the nervous phenomena, as we have said earlier, is very rapid under iodine. During the first night or two in the hospital sometimes we have found luminal 0.1 gm. ($1\frac{1}{2}$ grains) useful in securing rest and sleep. Other medication is rarely necessary. Digitalis has no place unless the heart is grossly insufficient and even then its value is uncertain as compared with iodine. The removal of the metabolic load by iodine helps the heart much more than any stimulation due to digitalis can possibly do.

When the symptoms, metabolism and pulse indicate a satisfactory remission the operation is done. Before it an X-ray of the mediastinum to exclude intrathoracic goitre and to note the size of thymus and heart is taken. The vocal cords are looked at. The patient is told about the operation the day before. No "theft" is attempted.

The preoperative preparation in our clinic disturbs as little as possible the patient's hospital routine. Effort is made to assure an adequate carbohydrate intake previous to operation. Preliminary skin preparation is omitted in severely toxic patients. The patient is usually given a sedative the night before operation, and is encouraged to take fluids up to within six hours of the time set for operation. Morphia is given two hours before the time set for operation, usually in a dosage of 15 mgm. ($\frac{1}{4}$ grain), and an hour later a second dose is given, varying in size according to the effectiveness of the first. Nitrous oxide and oxygen is at present the routine anæsthesia.

Other Methods of Treating Exophthalmic Goitre

In any severe disease of obscure origin a wide variety of therapeutic agents are bound to be used in the course of time, at least until a really effective one is found. Witness for example the multiplicity of ineffectual remedies advocated for pernicious anæmia and their disappearance since the specific effect of liver was discovered by Minot. The same is true of exophthalmic goitre, except that an agent equally as curative as liver in pernicious anæmia remains to be discovered. The effect of iodine in Plummer's dosage approaches but does not equal such specificity.

Many of the forms of treatment in Graves' disease are now obselete and need simply to be mentioned. Such, for example,

as the administration of the serum or milk of thyroidectomized animals, cytolytic sera, or the injection of boiling water into the gland, and numerous others of which space will not even allow mention. Recently alcohol has been tried in place of boiling water[35].

Rest. — The effect of rest alone, however, is worthy of more extensive mention. We fancy that no one will deny that proprolonged rest without other treatment in the majority of instances will be followed by a certain improvement and, if continued long enough, by recovery[36]. It is also a matter of common experience that many cases of exophthalmic goitre on first being put to bed will show a prompt improvement in symptoms and fall in metabolic rate before any drugs or other treatment is given. For example, Means and Aub[7] reported in 1919 an average drop of 14 points in the basal metabolic rate in six cases on rest in bed alone, and since then similar and occasionally somewhat greater drops have been observed in our clinic. Our experience in the main, however, has been that the drop is short lived, and that in the course of a week or less in most instances an approximately constant level of hypermetabolism is reached, which further rest does little to alter until after many months, or even years have passed; in other words, until the disease has run its natural course and so to speak burned itself out. To rely on rest as a sole method of treatment seems to us unwise. For one thing it is going to necessitate the expenditure of many months on an incomplete and uncertain cure, when symptomatic recovery is possible in a few weeks and with a high degree of safety by subtotal thyroidectomy in an iodine remission.

Endocrine therapy of various sorts has been tried. Thyroid itself is reported by some[44] to do good, by others[45], harm.

Shapiro[46], on the strength of Marine and Bauman's[47] finding that metabolism rises after resection of the adrenal cortex, has given a glycerin extract of adrenal cortex to patients with exophthalmic goitre. Such data, as he has published, impress us as distinctly inconclusive. Lastly, insulin[48, 49, 50, 51, 52] has been tried by several investigators; the results with this also are as yet difficult to interpret.

Treatment Directed against a Hypothetical Extra-Thyroid Cause. — Certain writers have much to say to the effect that the cause of exophthalmic goitre lies without the thyroid, which is very likely true, and that consequently the treatment should be directed accordingly. This would be very fine if we had the faintest notion where outside the thyroid this mysterious cause lies, but we have not. The sympathetic nervous system has been blamed, as we have already seen, and accordingly sympathectomies have been tried. This procedure, however, while it may diminish exophthalmos, has no apparent effect on the other features of the disease, and except as an occasional means of correcting extreme exophthalmos, has largely dropped out of sight.

A toxæmia arising from the bowel has been blamed for most chronic ailments, and exophthalmic goitre has not escaped. McCarrison[53] has advocated and claimed good results from the use of intestinal antiseptics. Since it is uncertain whether there are any drugs having an antiseptic action in the bowel, and since there is but little evidence that exophthalmic goitre originates from any error in the bowel, this form of treatment would seem to be of very questionable value. At least it is harmless. Protein shock also has been tried in exophthalmic goitre as in nearly every other chronic malady of unknown origin[54].

CASE NO. 13754. *Thyrotoxicosis appearing at the Menopause and Subsiding after Menopause was passed*

History and Examination. — Mrs. Hazel B., 46 year old graduate nurse, presented herself on December 17, 1934 at the advice of her physician, Dr. Howard B. Sprague, with the chief complaints of palpitation, increased irritability and nervousness. Her periods had been grossly irregular for two years, and she had had her last flow seven months previous to admission to the clinic. She had lost about 30 pounds in nine months and had noted excessive perspiration and sense of warmth. She had three bowel movements per day for nine months, which was a definite change in bowel habit for her. Her strength had so decreased that she was unable to do housework. Physical examination showed her to be a well-developed but thin woman who was definitely overactive, worried and flushed. Definite tremor was present. Her thyroid showed a slight diffuse enlargement of both lobes, the right being larger than the left. The gland was firm, compact, slightly irregular, but not nodular. No thrill was felt, but a characteristic pulmonic scratch was heard in the third left intercostal space. In addition her heart was rapid, and the first sound was forceful and accentuated. No evidence of cardiac insufficiency was found. The remainder of the examination was negative. There were no eye-signs.

Management. — A series of B.M.R.'s showed her to have a level of plus 25 to plus 30 (five tests), and she was placed on Lugol's solution, min. 5, t.i.d. on December 19, 1934. Nine days later the B.M.R. was plus 13, and on the 12th day of iodine therapy it was plus 11. She made a concomitant symptomatic improvement and started to gain weight rapidly. She was continued on the same dose of Lugol's solution and returned in one month's time with a B.M.R. of minus 2. She continued to gain weight and strength, and hot flushes became fewer and less severe during the succeeding four months and her B.M.R.'s remained at a minus level.

On June 6, 1935 iodides were discontinued because of excessive weight gain and also to determine whether her thyrotoxicosis was still active. She has been observed for 18 months off iodides and her B.M.R.'s have continued to range between minus 7 and minus 14 and she has had to limit her diet to control her weight. She has remained completely free of her thyrotoxic symptoms and her thyroid gland has decreased quite definitely in size.

Comment. — Data which is being accumulated gradually in our clinic at the present time (1938) indicates that, while typical cases of Graves'

disease occur at the menopause, quite often there is found a moderate to severe degree of hyperthyroidism associated with the menopause, which is transitory and rather well controlled by iodine medication. Typically the latter type of case is attended by only slight or no eye signs, a thyroid gland which is diffusely but only moderately enlarged and quite firm and a definitely elevated B.M.R., which responds in most instances remarkably well to iodine therapy. Many of the cases studied have shown rapid gain in weight and a drop in B.M.R. to substandard levels. In those instances in which we have complete data the cessation of the hot flushes and other manifestations of the menopause has allowed the omission of iodine therapy without the return of hyperthyroidism. We have come to regard this special class of patient as suitable for medical management, rather than surgical operation. Mrs. B. seems to be one of these.

Case No. 7793. *Anterior Pituitary Hyperthyroidism in a Patient with Acromegaly*

History and Examination. — Vincenza C., a 55 year old Italian woman, entered the hospital April 12, 1930 with complaints of nervousness and insomnia of about three or four months duration. She was conscious also of increased fatiguability, tight sensation in throat and excessive shakiness during excitement and exertion. Her vision had been failing, and she noted the recent development of headaches, increased sweating and a progressive increase in weight. Her weight five years before entry was 180 pounds and on entry was 250 pounds. Although acromegalization of her hands, feet and face were marked, the family had failed to note the change in her appearance, as it had developed so slowly. Pictures from an old album showed only slight evidence of acromegaly at the age of 45. Her appetite was very good. Catamenia started at 15, and menopause occurred at 50. She noted paresthesiæ of hands, and had moderate arthritic pains. She had considerable dyspnœa and palpitation.

Family History: One nephew had tuberculosis. No endocrinopathies known.

Past History: Irrelevant. Always enjoyed good health until present illness.

Physical Examination: Revealed an obese woman with obvious acromegalic features; large nose, prominent jaws and enlargement of hands and feet. Skin was coarse and moist, and moderate pigmentation was present. Blood pressure was 220/110. Cervical glands were enlarged, and parotid and submaxillary glands were increased in size. The parotid

on the left side was 6 by 6 cm. Heart was definitely enlarged (confirmed by x-ray), and a loud blowing systolic murmur was heard over the entire precordium, which was transmitted upwards into the neck vessels. Râles were heard at both bases of the lungs. Liver was enlarged and palpable. Perforated nasal septum was found.

Laboratory studies revealed a normal blood and urine. X-ray of sella showed definite enlargement, and typical acromegalic changes of spine and jaw, terminal phalanges and knee joints were demonstrated. Hinton and Wassermann tests were negative. Electrocardiogram was essentially normal except for left axis deviation. Blood sugar tolerance curve showed a somewhat decreased sugar tolerance. Curve rose to 227 mgm. in one and one half hours. B.M.R. was persistently elevated above plus 35.

The data were as follows:

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
Apr. 16	+43	78	106.0	
" 18	+30	72	104.0	
" 21	+45	76	102.9	
" 22	+37	72	103.1	
" 23				Lugol's m xx t.i.d.
" 24	+38	72	102.7	
" 25	+39	73	103.5	
" 26	+29	73	103.2	
" 28	+28	73	103.0	
" 29	+26	62	102.8	
" 30	+22	80	103.0	
May 1	+31	70	102.4	
" 2	+18	69	102.7	
" 3	+21	73	102.7	
" 5	+26	68	102.5	
" 6	+29	80	101.9	
" 7	+30	82	101.2	
" 8	+10	70	101.0	

Management. — The diagnosis, therefore, was quite definitely that of acromegaly with secondary hyperthyroidism of anterior pituitary type. A point of considerable academic interest is the fact that the hyperthyroidism responded in quite typical fashion to iodine therapy. As seen in the chart, the B.M.R. dropped from a plus 35 to 40 level to plus 10 in a period of 14 days on Lugol's solution, m. 20, t.i.d. Biopsy of the mass

in the cervical region revealed tuberculous adenitis, and iodine, therefore, was stopped. On the omission of iodides the symptoms of hyperthyroidism returned, and the B.M.R. rose to its pre-iodine level of plus 35 on June 5th after the omission on May 14, 1931, a period of about three weeks off iodine.

Subsequently x-ray therapy directed toward the pituitary gland was given with moderate success, but at no time in her course was this patient entirely relieved of her hyperthyroidism despite the repeated x-ray and iodine therapy. Finally, the cardio-vascular system has become the most prominent factor in her disability. Continued iodide therapy has not sufficed to maintain a lowered level of metabolism, and x-ray therapy of more intensive type than that given in previous courses is now being attempted (1938). We have not felt that thyroidectomy had much to offer this patient, but continued x-ray therapy over the thyroid is being used to control the thyrotoxicosis.

We have studied the thyrotropic hormone content of this patient's urine, and on several tests have found an amount which is above normal. The evidence that this patient has anterior pituitary hyperthyroidism seems to us to be quite complete.

Treatment of Exophthalmic Goitre in Children

Treatment of exophthalmic goitre in children, on account of the milder course, permissibly may be more conservative than in adults. As we noted earlier, the symptoms are less marked, and the course more definitely self limited. Subtotal thyroidectomy therefore probably will rarely be necessary, and there are certain obvious reasons why it is less desirable to deprive a growing child of five-sixths of his thyroid than an adult.

X-ray therapy would seem to be the method of choice, with thyroidectomy only in cases that did not show a satisfactory improvement after a reasonable length of time (three or four months). Rest, fresh air and an abundant, well-balanced dietary also should be insisted on.

Sequellæ and Their Treatment

Residual symptoms in patients treated surgically or by X-ray or otherwise are observed not infrequently. Most of these can be recognized as due to a return of thyrotoxicosis or to thyroid lack. It is even possible that the two may occur together. Such residual manifestations may come to the doctor's notice anywhere between one month to ten years after termination of treatment. It is in order to treat them in their beginning that watch is kept at the Massachusetts General Hospital clinic over all exophthalmic goitre patients that will so coöperate by means of repeated follow-up visits, every few weeks at first, then twice or once yearly.

In identifying the nature of these residua the basal metabolism is very helpful, but unless carefully correlated with the clinical picture, it is often misleading.

The simplest situation is the persistence of symptoms

similar to those before treatment. This is usual after hemithyroidectomy and occurs occasionally after subtotal thyroidectomy. Following operation the basal metabolic rate remains elevated, perhaps after a brief drop of a few weeks, and the usual symptoms of the disease continue, although almost invariably in a milder form. When the elevation once occurs, it is likely to persist indefinitely in the absence of further treatment, and it is a sign that the removal of the thyroid tissue has not been adequate. On this account, it is extremely desirable for the surgeon to see the late results of treatment, so that he can check up on the sufficiency of his removal of the gland. Should the metabolic rate persist for some months within normal limits, a return of hyperthyroidism with its symptoms is rare and is usually associated with further hyperplasia of the remaining thyroid tissue. Thus we can distinguish a persistence of thyrotoxicosis due to inadequate operation and an actual recurrence of the disease with hyperplasia of the remaining gland tissue. Of the latter condition we have seen only two instances, in which after being apparently cured for several years, a definite increase in the size of the remaining thyroid tissue took place with recurrence of symptoms. Both these patients were relieved after further operation. Regeneration of thyroid tissue after subtotal thyroidectomy for exophthalmic goitre is probably more common in goitrous than in non-goitrous regions.

After inadequate relief of symptoms, whether treated by hemithyroidectomy, subtotal thyroidectomy, or X-ray, we have rarely seen the metabolic rate exceed plus 50 per cent., and usually when elevated it is in the neighborhood of plus 20 per cent. to plus 40 per cent. Plummer's so-called crisis status we have never observed in marked form three months or more after operation or after adequate X-ray. Exophthalmos rarely in-

creases after thyroidectomy, although it sometimes fails to decline. In successfully treated cases it is often one of the last signs of the disease to disappear.

The peculiar nervous phenomena of exophthalmic goitre may persist for years after the treatment was begun or may return after an interval of complete relief. The latter occurrence is more common after X-ray treatment than after subtotal thyroidectomy, although in most instances where successful relief of symptoms follows radiation it is permanent. If marked persistence of symptoms with elevation of metabolic rate is present, it is an indication for further destructive treatment. Since secondary operations following subtotal thyroidectomy are difficult, it has been customary to make a trial by X-ray treatment before advising further surgery.

The effect of iodine upon these residual phenomena is most interesting, particularly in those cases with relatively slight or no elevation of the basal metabolic rate. In our experience it seldom fails to have a prompt and striking effect, consisting in an almost immediate and complete disappearance of all the subjective and most of the objective manifestations, regardless of the time which has elapsed since the onset of the disease. This is accompanied invariably by a drop in metabolic rate, so, be the condition one of hyperthyroidism or dysthyroidism, the effect of iodine is anti-calorigenic in either case. Plummer, it will be recalled, postulates a bad hormonal product responsible for the peculiar Graves' manifestations, in other words a dysthyroidism. The manufacture of this fails to take place in the presence of adequate iodine. As we explained earlier, we are not entirely content with this theory but are unable to supply a better. We can say, however, that if dysthyroidism occurs at all, it may in some cases persist for many years, in one

case, for example, we have seen the metabolism drop and the symptoms clear as late as seventeen years after the onset of the disease (Case No. 68).

CASE NO. 68. *Exophthalmic Goitre of Extraordinary Chronicity. Astounding Lack of Cardiac Damage Therefrom; also Illustrating Late Effect of Iodine*

History and Examination. — This patient, a married Russian Jewess, mother of two children, both tuberculous, resident in Massachusetts since 1897, developed, according to the story obtained at the time of her first entry to this hospital, December 9, 1912, typical exophthalmic goitre in 1909 at the age of 28. At the time of this first entry she had clearly been thyrotoxic for three years, though never incapacitated thereby. The cardinal manifestations of Graves' disease were all present. No inciting or predisposing factor could be discovered.

Management. — At the first entry (1912) operation, "preliminary ligature under local anæsthesia, then right hemithyroidectomy", was advised. The patient refused and was discharged and for a couple of months was given quinine hydrobromide and observed in the out-patient department. Nothing very striking resulted.

On July 20, 1915 she was admitted again to this hospital with a story of gradual increase in symptoms. All of the cardinal manifestations of Graves' disease were still present. The size of the heart by percussion at this time was 3.5 cm. to the right, 10.5 to the left. A blowing systolic murmur was heard at the apex. The pulse varied between 90 and 100 and was uninfluenced by digitalis. The blood pressure was 140/80. X-ray treatment of the thyroid was begun, and on September 4, 1915 she was discharged to the out-patient department to have this continued.

Our basal metabolism observations, which are all shown in the chart (Fig. 34), did not begin until September 12, 1916, that is to say in the eighth year of her disease. At this time she had had nine X-ray treatments with no noteworthy result. She was subsequently given thirteen more.

The metabolic rate figures indicate that this prolonged irradiation was largely devoid of effect, and the same conclusion was reached from the symptomatology. On February 16, 1917 she was sent into the hospital and operation was again advised, but refused. The heart measurements at this time on percussion were given as 3.5 cm. to the right, 12.5 to the left. An electrocardiogram showed normal rhythm and slight left ventricular preponderance. The T wave was not high. Blood pressure was

145/75. The pulse varied between 80 and 90 up until November, 1926, when she was first given Lugol's solution; there was only little change in her condition. She was seen often enough to warrant the conclusion that a state of continued thyrotoxicosis had existed during a period of seventeen years. During ten years of this time in spite of her disease she had supported herself and two children, her husband having died in 1912. In 1922 she felt or thought she felt better, although this was not reflected in her metabolism, and she remarried. This did not lighten her cares especially as her second husband had six children.

She was then lost sight of until March 23, 1925, when she returned in

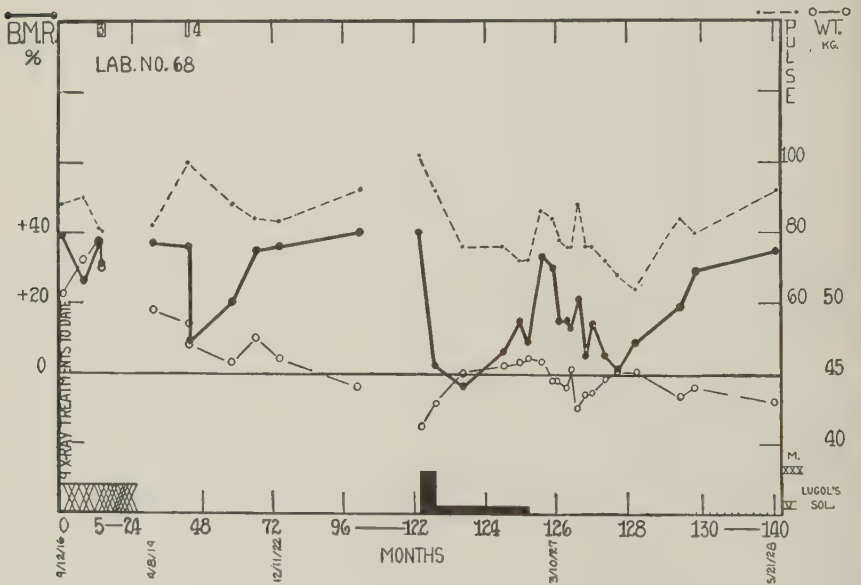

FIGURE 34. *Exophthalmic Goitre* (*Case No. 68*). Extraordinary chronicity, and showing the late effect of iodine.

response to a letter. The clinical manifestations and metabolism level were quite unchanged. There was marked skin atrophy and numerous telangiectases over the neck and upper chest due to the irradiation. The heart by percussion measured 2 cm. to the right, 12 to the left. The blood pressure was 150/82. There was no question but that she was thyrotoxic. Operation was again advised and refused. Her heart seemed to be bearing the prolonged strain remarkably well.

She was next seen November 17, 1926, reporting on her own initiative

and saying that finally after seventeen years of exophthalmic goitre she would like an operation. It was decided, however, to try what could be accomplished on Lugol's solution 2 c.c. (30 minims) per day. In twelve days there was a truly remarkable change. The metabolism at once dropped to normal, the exophthalmos grew less and the symptoms disappeared. She said she felt better than at any time since her disease began. The drug was continued until February 18, 1927 when it was stopped. The metabolism promptly returned to its previous level and the symptoms recurred but more slowly. By March 10, 1927 they were about as before the iodine was begun. Lugol's solution was therefore resumed but this time in the dose of 0.5 c.c. (7 minims) per day. From March 16, 1927 to May 17, 1927, during which time this small dose was continued, the metabolism varied between +1 per cent. and +21 per cent. and the symptoms were definitely less.

On May 17, 1927 Lugol's solution was omitted for the second time, and metabolism slowly rose to +29 per cent. on July 5, 1927 and the symptoms increased slightly but not to the intensity of November, 1926.

She was seen next after the lapse of another year May 21, 1928, having in the mean time taken Lugol's solution at irregular intervals, not she believed over a few drops per month. Her condition was not greatly altered. Well marked exophthalmos remained and lid lag. The goitre was smaller than in 1926 and was hard and firm. The skin was warm and moist, but there was no tremor.

Comment. — A case of extraordinary chronicity, veritable chronic exophthalmic goitre, with striking relief from iodine late in the course of the disease, and remarkable lack of cardiac damage. We must regard this as an instance in which the cause of the Graves' disease persists, although from time to time iodine will correct its effects.

The fact that iodine does not influence hyperthyroidism following thyroid ingestion is a point in favor of dysthyroidism in exophthalmic goitre, but if dysthyroidism occurs it must be admitted that the bad product is quite as definitely calorigenic as the normal.

Perhaps the most important cases to identify correctly are those in which the metabolic rate is normal, but in which nervous or psychic symptoms and exophthalmos persist or recur. These people, Plummer would say, have the dysthyroidism and the symptoms in consequence, but their metabolism is not up

because the total manufacture of calorigenic substances by the thyroid is not in excess of normal. When iodine is given to such persons the metabolism will drop from a normal to a subnormal rate. This we have observed repeatedly, and in a case shown one of us by Plummer at Rochester, and in another referred to us by him for treatment, a state of actual hypothyroidism developed while on iodine, so that thyroid had to be given as well.

The use of iodine late in the disease therefore, after the direct attack upon the thyroid has been completed, is of great importance, but by no means easy to regulate.

To use it intelligently both careful observance of symptoms and metabolism determinations are necessary. The chief aim should be the control of symptoms not the maintenance of any particular metabolic rate, but knowledge of the latter is desirable in deciding whether thyroid medication is necessary also (Case No. 1786).

CASE NO. 1786. *Exophthalmic Goitre Treated by Irradiation and Iodine with Some Striking Iodine Relationships*

History and Examination. — A doctor's wife of 46, resident in western Massachusetts, consulted one of us (J. H. M.) first on September 12, 1923. Her symptoms of Graves' disease had been noted fourteen months earlier and consisted in prominence of right eye and goitre, together with nervousness, insomnia, increased irritability and rapid pulse. A diagnosis of thyrotoxicosis had been made in December, 1922 and a basal metabolism had shown a rate of plus 26 per cent. She had been advised to rest three months in bed and did so, following which there was very definite improvement in symptoms. At the time she was first seen by one of us, she had very few subjective complaints. There was nothing in the past history that seemed predisposing. She had had three children in rapid succession about twenty years before and no other pregnancies. Her catamenia had stopped at the age of 43. There had been no discharge since.

Examination. — This showed moderate exophthalmos more marked on

the right, moderate tremor, and warm moist skin. There was moderate symmetrical fullness of her thyroid with bruit. The impression was that of typical exophthalmic goitre of rather slight intensity.

Management. — Because of the apparent mildness of her disease, it was thought legitimate to treat her by X-ray. It was also considered advisable to give iodine at the same time. These were both accomplished without hospitalization, the patient being at home and following her usual occupation. The metabolic rates and therapy are indicated in the chart (Fig. 35).

On fifteen, then ten drops of Lugol's solution per day, there was a very rapid and marked improvement. Her pulse quickly assumed a

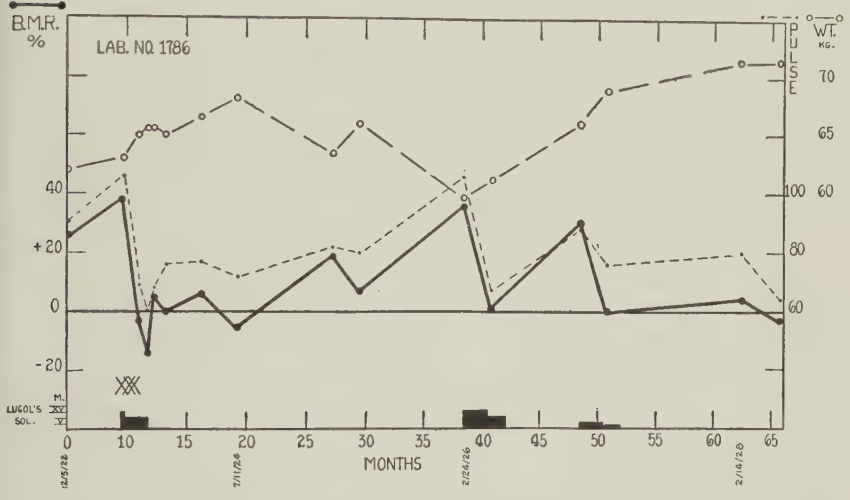

FIGURE 35. *Exophthalmic Goitre (Case No. 1786).* Treated by iodine and X-ray and showing late effect of iodine.

normal rate and her sleep became much better. On October 15, 1923, examination showed the eye signs about the same, the goitre slightly larger, but the tremor and tachycardia had gone. Furthermore, the bruit over the thyroid had completely disappeared. She had had at this time not only Lugol's solution for over a month, but three X-ray treatments as well. She claimed to have no symptoms and to feel better than she had for years.

On November 5, 1923, the basal metabolism was quite normal, the pulse also, and she had gained weight. On November 26, 1923, the improvement was described as "truly remarkable". The metabolism

had dropped to a subnormal level, and Lugol's solution was omitted. Three weeks later the metabolism had risen to plus 5 per cent. There was no tremor but a slight bruit on the left side of the thyroid only.

She remained essentially well for another year. On December 10, 1924, her only complaint was occasional hot flashes. Exophthalmos of moderate degree was the only clinical relic of the Graves' disease discoverable. The goitre had gone; there was no tremor.

In January, 1925, she had an acute infection called "grippe", which was followed shortly by what was taken to be scarlet fever. These infections were followed by a marked prostration. When seen on May 22, 1925, exophthalmos was as before; the thyroid showed very slight fullness with bruit, this time on the right only.

The heart action was increased and there was slight tremor. The impression was that she was mildly thyrotoxic, although four days later the basal metabolic rate was but plus 7 per cent. There was some suggestion of gallbladder disease. The heart was slightly enlarged, and X-ray showed a tortuous aorta. The blood pressure was 150/80. Her complaints were chiefly asthenia and palpitation.

Quinine hydrobromide, 0.3 gm. (5 gr.) t.i.d., was given through June and July, 1925. Apparently it helped her palpitation somewhat. In August, 1925, the eyes were as before but the goitre and tremor had disappeared.

She was seen next on Februrary 20, 1926. She reported herself as better. She had lost some weight in the autumn but not since. There was some discomfort in the right upper quadrant of the abdomen. She also complained of polyphagia and polydipsia. Urine was normal.

On February 24, 1926, however, the metabolism and pulse were both elevated, and in consequence she was started again on Lugol's solution. She had had none since November 26, 1923.

On April 16, 1926, having taken the drug cautiously 1 c.c. (15 minims) a day, she reported herself much better. The improvement was noticeable in about two weeks. Her eyes she thought were less prominent, and she was sure they were more comfortable. She returned to her home and continued on Lugol's, this time 0.6 c.c. (10 minims) per day.

On June 23, 1926, she wrote that toward the end of May she had developed spots on her face which her local physician thought due to iodine which he advised to be stopped.

On December 26, 1926 she presented herself complaining of some recent attacks of frontal headache. These apparently were of a peculiar sort which she was at a loss to describe, not like ordinary headache, rather pounding in character but with no measured beat. Head was not lame

or tender. There was no visual disturbance nor aura. These attacks lasted a few hours at a time. In other respects she claimed to feel very well. Her hot flashes and palpitation had stopped. There was slight dyspnœa on effort. There was no goitre. There was slight tremor. The metabolism two days later was plus 30 per cent. and the pulse 88. It seemed evident that she was again slightly thyrotoxic. Lugol's solution, 0.3 c.c. (5 minims) per day, was ordered.

Two months later, February 25, 1927, she presented herself. The iodine she said had "produced a profound relaxation, a pleasant relaxation. Just as if you had been all screwed up before and under tension". This feeling all stopped on iodine. In other words, on iodine she felt "perfectly normal". The peculiar headaches were relieved. Along with the physical relaxation there was a profound mental relaxation as well. Worry ceased; ability to do brain work increased. Two weeks after the iodine was started, she noted swelling in her thyroid, chiefly on the right, soft and non-tender. She kept on with the iodine for another two weeks and then developed some acute abdominal distention, relieved by castor oil. The next day both breasts became tender and spots appeared upon them and on the abdomen. She started taking iodine every other day and found the days she took it her breasts were tender, the days she did not they were not. The basal metabolism on February 26, 1927 was 0. It was decided that she needed some iodine in order to keep her Graves' manifestations in abeyance, also that the dose must be regulated to avoid symptoms of iodine poisoning. She was instructed to experiment with the dose and note effect. Two drops of Lugol's solution a day were suggested.

On May 30, 1927 she reported that she was feeling better than for years. She took iodine only when she felt a headache coming on and then took three drops a day for three days which apparently relieved her.

June 2, 1928 we heard from both her and her doctor. She had had no iodine for a year and been essentially symptom-free. The metabolism was normal. Some residual exophthalmos was the only remaining manifestation.

Comment. — There are many instructive features to this case, chiefly those connected with the use of iodine. In the first place, it is interesting to note that the first symptom was unilateral exophthalmos. This sometimes happens. The initial thyrotoxicosis was relieved by iodine plus X-ray. The very rapid relief of symptoms at the beginning was undoubtedly due to iodine. The subsequent absence of noteworthy thyrotoxicosis for nearly two years may be ascribed to X-ray.

The enlargement of the thyroid and disappearance of bruit with the

first course of iodine is of interest. The action of iodine in Graves' disease is accompanied by a decrease in hyperplasia and increase in colloid. With the latter the size may increase as here. With the former the circulation declines, and that is undoubtedly the cause of disappearance of the bruit as here.

Under the first course of iodine the metabolism sank to a subnormal level. This phenomenon we are seeing quite often. It may mean that the patient normally has a metabolic rate below the average for her age and sex. This first onset of Graves' disease in this case came near the menopause, the relapse after a series of infections. The chief point of interest with regard to the relapse is the extraordinary symptomatic improvement under iodine, particularly in the mental symptoms.

This effect of iodine on the mental symptoms in exophthalmic goitre was one of the points stressed by Plummer. It is no doubt striking and in our experience may occur late as well as early in the disease.

During the year 1927–28 the disease in this case seems to have finally burned out, iodine being no longer necessary to hold the symptoms in abeyance.

About the proper dose of iodine in the late stages we are in doubt. Work on this is actively under way at present. In most instances five drops of Lugol's solution once daily should be enough. Some patients may require ten, others only one or two. The doctor probably will have to discover the dose for the given patient by experiment.

This, however, brings us to the next important sequellæ of Graves' disease, hypometabolism and myxœdema. These terms are not synonymous. The symptoms of true myxœdema are well known and will be discussed in a later chapter, but here it may be said that they may occur during or after exophthalmic goitre in cases treated by surgery, by X-ray or by other means. When they do occur, the basal metabolism generally is found depressed to a level of minus 30 per cent. or 40 per cent., and thyroid in adequate dosage will promptly abolish them. The regulation of thyroid dosage will be discussed in the chapter on myxœdema and need not be given here; it is no different

in myxœdema following exophthalmic goitre from that in spontaneous myxœdema. Lahey[32] is of the opinion that the incidence of postoperative myxœdema has increased since the preoperative use of Lugol's solution was introduced, because the thyroid tissue remaining has been rendered less active by the iodine treatment.

There is another group in which after any of these forms of treatment, though perhaps most frequently after thyroidectomy, basal metabolism sinks to a low level, but the clinical signs of myxœdema do not appear. W. O. and P. K. Thompson[55] have recognized clearly this type and collected a series of forty-eight cases from the Massachusetts General Hospital clinic. In some the low rate is temporary, in others permanent. Sometimes low rates with myxœdema give way to low rates without it, and sometimes even typical myxœdematous manifestations spontaneously disappear, they having arisen as a sequel to exophthalmic goitre. We have, in other words, a type of temporary myxœdema, which so far as we are aware, does not occur otherwise than after Graves' disease.

The significance of low rates without myxœdema is not clear. Some writers have considered hypometabolism as synonymous with hypothyroidism, and consequently have labelled these cases atypical forms of the latter[56]. The correctness of such an interpretation is questionable. Since metabolism laboratories have been in vogue, most observers have found certain persons, apparently normal or with ill defined abnormalities chiefly of a neurotic nature, who constantly exhibit lowered basal metabolism. When symptoms are present in these people, they are usually in no respect those of myxœdema. On the contrary, although metabolically subnormal they are apt to be nervous and fidgety.

Plummer[56] has described them as psychoneurotics with low metabolism, strong emotions, weak wills, dysmenorrhœa, achlorhydria and arthritis. We have seen persons possessing all of these qualities except that the gastric contents has not been studied. The chief reason for saying these people are very likely not hypothyroid is that giving them thyroid often makes them worse. Unfortunately we have no data, except in a few accidental instances, on the original basal metabolism in persons who later develop Graves' disease. It has been suggested that the non-myxœdematous low metabolic rate cases (perhaps congenitally so) are unusually susceptible to Graves' disease, and that the low rate seen after Graves' disease in such people is merely a return to what is for them a normal, or at least an habitual level of metabolism.

Whatever the explanation, the therapeutic hint is clear, and that is that low metabolism is not per se an indication for thyroid administration. The clinical symptoms of myxœdema are the indications, not the existence of hypometabolism. If these points are borne in mind together with the iodine relationships given above, better success will be had in the late treatment of exophthalmic goitre.

Some illustrative cases will follow which may make these matters clearer.

Case No. 4103. *Exophthalmic Goitre with Drop of Over 100 Points in Basal Metabolic Rate in Two Months after Subtotal Thyroidectomy and Iodine.*

History and Examination. — An American housewife of forty-four had had the classic symptoms of Graves' disease for a year developing during the course of a pregnancy and getting gradually worse since. Examination on July 16, 1926 showed a somewhat emaciated woman with marked exophthalmos, slight goitre, but with bruit, violent heart action and tremor.

Management. — It was clearly moderately severe exophthalmic goitre and after iodine preparation, subtotal thyroidectomy was done in one stage. The portion of thyroid removed, isthmus and a part of each lobe, on section showed a translucent, brownish gray surface. Microscopically the follicles were distended with colloid and did not show the hyperplasia characteristic of exophthalmic goitre. The various events are indicated in the chart (Fig. 36).

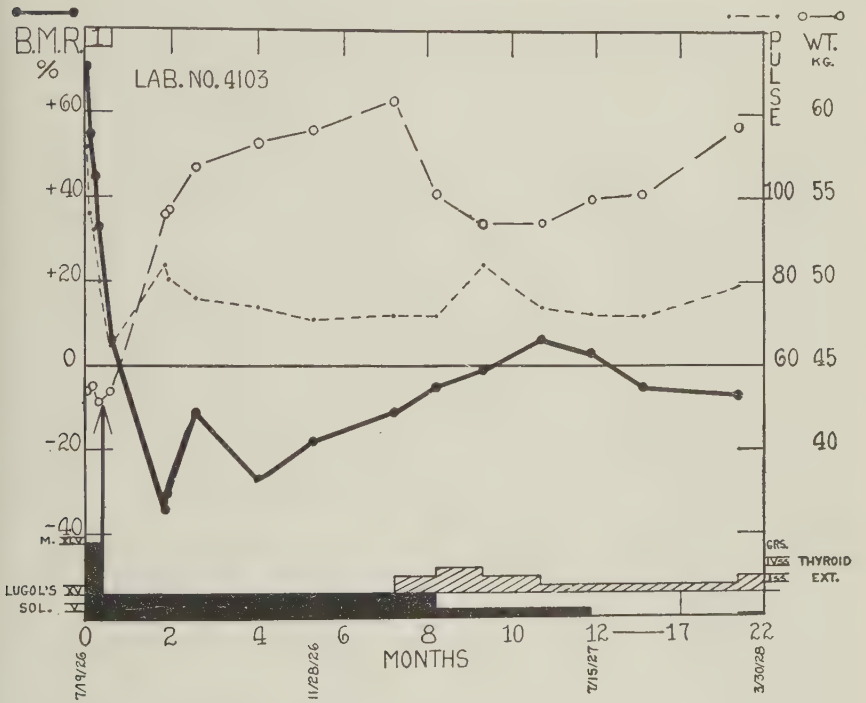

FIGURE 36. *Exophthalmic Goitre (Case No. 4103).* Showing a drop to a subnormal level following subtotal thyroidectomy and iodine.

Following operation the basal metabolism dropped to a markedly subnormal rate and coincident with that there slowly developed symptoms and signs suggestive of myxœdema. Thyroid was therefore given under which these manifestations disappeared. This drug has been continued to date in sufficient dosage to maintain a normal metabolism. On this régime for over a year she has had symptoms neither of hypo- or hyperthyroidism.

CASE NO. 4102. *Exophthalmic Goitre with Residual Thyrotoxicosis After Subtotal Thyroidectomy with Standard Metabolism Dropping to Substandard Level on Iodine*

History and Examination. — A twenty-two year old American, mother of two children, presented herself on July 23, 1926 with all the cardinal manifestations of exophthalmic goitre. The goitre had been noted for two months, and the symptoms of thyrotoxicosis had rapidly developed during

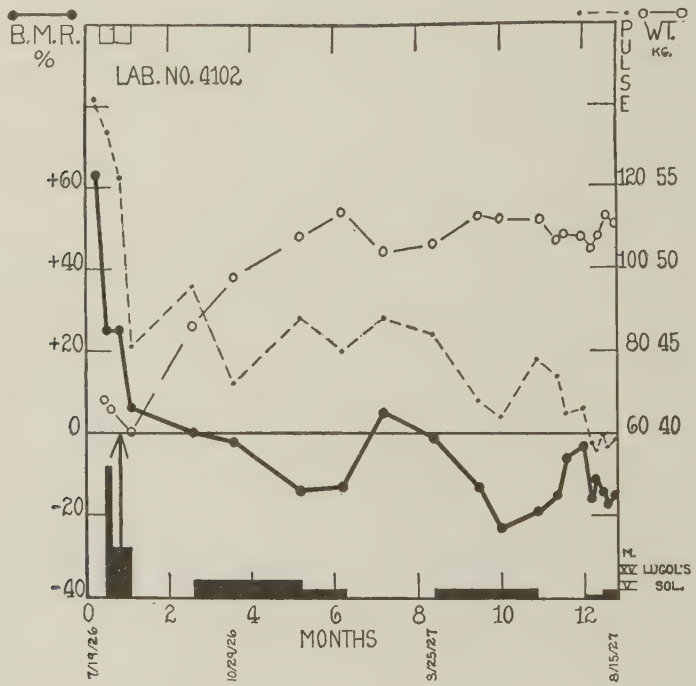

FIGURE 37. *Exophthalmic Goitre (Case No. 4102).* Postoperative drop to a low level of metabolism under iodine treatment.

that time. The exophthalmos was slight but the restlessness very marked, and the impression was that the degree of intoxication was severe.

Management. — She was given Lugol's solution in the customary manner as shown in the chart (Fig. 37), and had a very striking remission.

On August 8, 1926 a subtotal thyroidectomy was done under ethylene anæsthesia. The tissue removed showed the usual follicular hyperplasia. She made a good operative recovery, and five days after

operation Lugol's solution was omitted. Several weeks later it was given again for several months, and during this period the metabolism fell to a somewhat subnormal level, but rose again when Lugol's was omitted. This was repeated twice, the metabolism in each instance being lower while the patient took iodine than when she did not.

Comment. — This case is presented to illustrate very strikingly the effect of iodine in residual thyrotoxicosis. There were definite symptoms of nervousness and asthenia here for a period of over a year following the operation, which could be abolished by giving Lugol's solution. There also is clearly a striking difference in level of metabolism when taking iodine and when not. The rates observed while the patient took iodine we believe to represent her own true normal. We further believe that she was mildly thyrotoxic with a rate not above standard, but supernormal for her. These swings on and off iodine will probably continue to be produceable until the disease burns itself out, when a permanent low rate of between minus 15 per cent. and minus 20 per cent. will establish itself.

Case No. 4035. *Exophthalmic Goitre Treated by X-ray Then Operation and Followed by Mild Transient Hypothyroidism*

History and Examination. — A girl of nineteen, resident of New York City, was first seen June 18, 1926. She had had a goitre for two years and thyrotoxic symptoms including exophthalmos for eighteen months. At the onset of these a course of X-ray treatment had been given in New York which apparently had produced some improvement. At the time we saw her, there was some residual thyrotoxicosis, and two exposures in a second series of X-ray had been given. We found moderate exophthalmos, slight thyroid fullness with faint bruit, moderate tremor, and warm moist skin. There were some slight telangiectases and X-ray erythema over the neck.

Management. — It was clearly a case of mild exophthalmic goitre in a rather stationary state developing possibly in a previous simple colloid goitre of adolescence. The X-ray treatment previously given may very well have ameliorated the condition but had not cured it. On this account, and also because the skin changes contra-indicated further irradiation, the usual surgical program was advised. Lugol's solution was given with a satisfactory response and on June 29, 1926 a subtotal thyroidectomy under ethylene was done. The tissue removed showed the usual hyperplasia of exophthalmic goitre.

The metabolic data are as follows:

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
Jun. 18, '26	+36	128	61.7	
" 28, '26	+15	96	63.5	Lugol's solution since last note.
" 29, '26				Subtotal thyroidectomy.
Jul. 8, '26	− 6	84	63.0	
Sep. 9, '26	−25	76	61.9	Lugol's solution 0.15 c.c. (2 minims) per day since last note; omitted. Thyroid 0.2 gm. (3 gr.) begun.
Oct. 21, '26	+ 5	84	61.6	Thyroid omitted.
Jun. 23, '27	+ 7	96	61.5	Thyroid 30 mgm. (½ gr.) per day for 3 wks., stopping 1 wk. previous to the observation.
Sep. 30, '27	− 5	84	65.1	Lugol's solution 0.3 c.c. (5 minims) per day since last note.

She responded well to operation and her thyrotoxic symptoms rapidly disappeared. The exophthalmos decreased but did not go entirely. In September, 1926, however, she developed some lethargy and asthenia and definite chilliness. The skin was not harsh; it was cool and moist. There was no goitre nor tremor. She had not gained weight, although the metabolism had dropped to minus 25 per cent. She had taken Lugol's solution 0.15 c.c. (2 minims) daily since leaving the hospital. It was thought that there was a slight element of hypothyroidism. Lugol's solution was omitted and thyroid (Burroughs-Wellcome and Co.) 0.2 gm. (3 gr.) per day was begun.

She was seen a month later; the hypothyroid symptoms had disappeared and the thyrotoxic had not returned. The metabolism was plus 5 per cent. (October 21, 1926), and she appeared entirely well save for a slight residual exophthalmos. There was a tendency to keloid formation in the scar.

In June, 1927 she showed essentially no symptoms of hypo- or hyperthyroidism. Her first catamenia since the operation occurred. There still was some slight exophthalmos and lid lag and slight tachycardia on account of which she was given Lugol's solution 0.3 c.c. (5 minims) per day, which she continued to take for three months. During this time she gained weight and felt perfectly well. The lid lag disappeared; slight prominence of the eyes remained the sole relic of her disease.

Comment. — This case is presented as an instance of very mild, temporary myxœdema following operative treatment of exophthalmic goitre. That it was true hypothyroidism we believe is likely, in view of the fact that a year later iodine failed to depress the metabolic rate to a subnormal level, showing that she had no residual thyrotoxicosis, and that her true metabolic rate was not below the average.

Among other sequellæ of importance which may require treatment is obesity, particularly in postoperative cases but also in others. Body weight depends of course upon the balance between intake and outgo of energy. During the early stages of Graves' disease the balance is generally in a negative direction, and loss of weight is the rule. Under treatment, even though metabolic rate remains elevated, a rapid shift may take place and rapid gain in weight result. This possibility should be borne in mind, the weight carefully observed, and any tendency to gain checked by diet restriction before a marked obesity has developed.

CASE 4199. *Exophthalmic Goitre; One Stage Subtotal Thyroidectomy with Prompt Relief; Startling Gain in Weight after Operation*

History and Examination. — A nineteen year old American factory girl entered the hospital September 24, 1926 with a story of thyrotoxic symptoms together with goitre for a year, but the former had been getting much worse in the last two months during which time she had lost 8.5 kg. She had slight exophthalmos and other classic signs, the intensity of which, together with that of the symptoms, led to the conclusion that her disease was of mild or moderate intensity. This, however, was belied by the metabolism level which was observed sufficiently frequently to be accurate and which denoted a more severe degree of intoxication. It is likely that she was in or approaching a toxic crisis which the prompt administration of Lugol's solution forthwith aborted.

Management. — After the drop shown in the chart (Fig. 38) together with an equally striking improvement in symptoms, subtotal thyroidectomy was done in one stage under ethylene on October 13, 1926. There was considerable fever for three days following operation but after that an uneventful convalescence.

The patient remained under observation after operation for 13 months and during that time has remained for the most part free from symptoms. About five weeks after operation there was very slight asthenia and tremor. Aside from that, plus occasional slight nervousness, there have been no symptoms suggestive of Graves' disease.

Comment. — The high metabolism, out of proportion to her clinical symptoms, and the behavior of her weight postoperatively, are the points we wish to stress here.

This patient like many others in our experience gained much weight, became obese in fact, after operation. Along with this for a time, chiefly

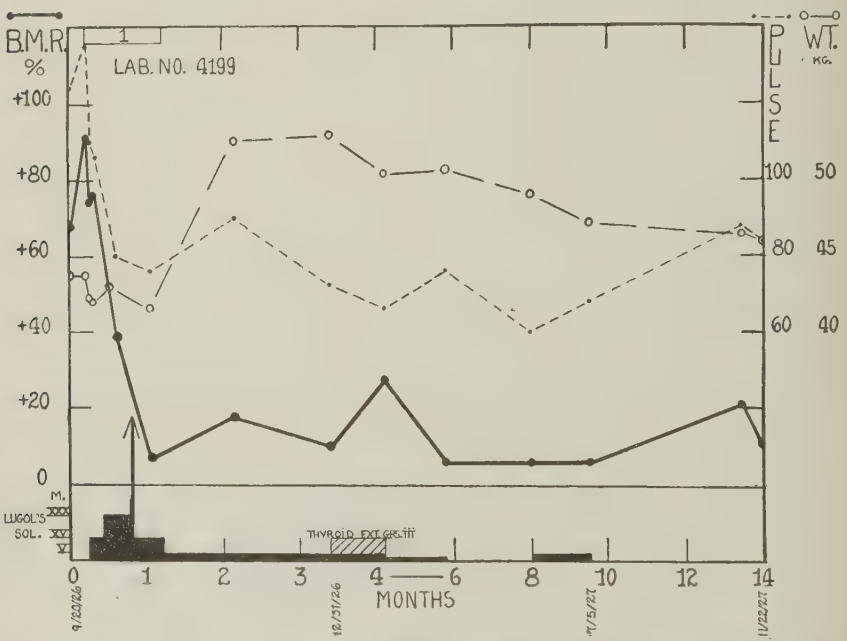

FIGURE 38. *Exophthalmic Goitre (Case No. 4199).* One stage subtotal thyroidectomy in an iodine remission.

between November 24, 1926 and December 31, 1926, her face exhibited the type of puffiness that renders it round and moon like (Thompson) for which a short course of thyroid was given. The significance of this puffiness is not clear. It may be a hypothyroid manifestation of some sort, but if so it occurred in this case with no hypometabolism. It is perhaps better regarded as a result, as is likewise the gain in weight, of a recently revolutionized energy exchange.

During the period of development in exophthalmic goitre there is generally loss of weight. When the toxic crisis has passed spontaneously or as a result of treatment, frequently there is a corresponding gain and sometimes a gain greater than the previous loss. The energy balance has suddenly shifted from the negative to the positive, and this may occur even when the metabolic rate is still well above normal.

Sometimes rapidly developing obesity demands treatment per se; dietetic if the metabolism is not depressed, reinforced with thyroid when the metabolism is low.

Finally, serious residual exophthalmos deserves mention among sequellæ for it still is seen occasionally, though with modern methods of treatment it is far less frequent than formerly. There is no doubt that it is affected beneficially by iodine even after it has been present for years. This was among Plummer's[57] claims for the action of Lugol's solution, and we have had an opportunity to confirm it in several cases. In intractable cases in former days, as we have already noted, cervical sympathectomy sometimes caused some retrogression of the globes. In the days before Lugol's solution there was treated in the Massachusetts General Hospital clinic by X-ray therapy, for the time being with apparent improvement, a woman with exophthalmic goitre who subsequently developed such extreme exophthalmos that both eyes had to be enucleated at another hospital. After the right eye had been removed, removal of the left superior cervical ganglion was done in an unsuccessful attempt to save the left eye.

Complications and Their Treatment

Cardiac Complications

Of all organs of the body that which is most likely to suffer from prolonged hyperthyroidism is the heart. So important is this fact that we find the terminology of cardiologists includ-

ing the term thyroid heart disease. Hypertrophy is seldom marked, but disturbances in rhythm are frequent and congestive failure not uncommon. Dr. Paul D. White[58] tells us that in a series of 2693 of his private cardiac patients, he made the diagnosis of thyroid heart disease in 26. Of these 10 had auricular fibrillation, 3 paroxysmal in type and 7 permanent. One patient had paroxysmal tachycardia alone, and another auricular premature beats alone. One had angina pectoris. One of those with fibrillation also had congestive failure and 13 had no special functional disturbance. These data of course represent the aftermath, the degree of cardiac crippling as seen by the cardiologist as a sequel to toxic goitre.

In the thyroid clinic, cardiac disturbances in toxic goitre are encountered much more frequently than they are by the cardiologist, but fortunately with the cure of the thyrotoxicosis they for the most part disappear. Nevertheless the observance and care of the heart is an important phase in the management of toxic goitre.

The principles involved are no different from those of the treatment of any other form of heart weakness. Ordinary muscular insufficiency with acute or chronic passive congestion is occasionally seen[59], so too are disturbances in rhythm such as fibrillation of the auricles, either paroxysmal or continuous[60, 61].

The point of fundamental importance to bear constantly in mind is that in thyroid heart disease to a greater extent than in almost any other variety we can remove promptly the chief load upon the heart, namely the hypermetabolism and the extra circulation it calls for. Medical opinion has reversed itself in this regard, for we find Jackson and Mead[38], for example, in 1908 concluding that, "organic heart changes and bad general condition surely are contra-indications to operation", whereas

it is now believed[62, 63] by many (including the writers) that the existence of serious heart embarrassment during the course of any thyrotoxic state rather increases the desirability of prompt thyroidectomy. When a heart is laboring unduly, lightening its load will do more than anything else to improve its action. In exophthalmic goitre this can be done by adequate iodine administration. As the metabolism drops, signs of heart failure generally will improve, and subtotal thyroidectomy can then be carried out with a high degree of safety, and following it the cardiac manifestations generally will disappear.

Digitalis probably is desirable in such patients with thyrotoxicosis as have true congestive failure. The tachycardia directly due to thyrotoxicosis is uninfluenced by digitalis. If there is an addition to the already hurried rate purely due to cardiac insufficiency, digitalis may bring about some slight slowing. When used at all we believe that it should be given in full doses, our rule being 0.1 gm. ($1\frac{1}{2}$ grain) for every ten pounds of body weight for the digitalizing dose, and 0.1 gm. ($1\frac{1}{2}$ grain) per day for the maintenance dose. Cardiac weakness as a late manifestation or sequel to exophthalmic goitre is seen occasionally, and is treated like cardiac weakness from any cause. It is not common after exophthalmic goitre, but is rather more so in adenomatous goitre with hyperthyroidism, which will be discussed later.

Auricular fibrillation occurs in both exophthalmic goitre and adenomatous goitre with hyperfunction, being somewhat more common in the latter. It is usually paroxysmal at first. A paroxysm frequently follows operation, but usually does not persist. When it does persist, quinidine may be employed in an attempt to restore normal rhythm. A trial dose of 0.2 gm. (3 grains) can be given in the afternoon, and watch kept for

toxic symptoms such as urticaria, diarrhœa, nausea and vomiting, or ringing in the ears. If these do not appear, the following morning the drug may be given in doses of 0.4 gm. (6 grains) every two hours until the rhythm changes, or until toxic symptoms begin. Up to 4 gm. (60 grains) may be given daily and continued for a week before a failure is declared. If normal rhythm is restored, a maintenance dose of 0.2 to 0.3 gm. (2 to 3 grains) three times a day should be kept up for a fortnight. If the first course proves a failure, a second attempt should be made in two or three weeks.

CASE NO. 3187. *Exophthalmic Goitre with Paroxysmal Auricular Fibrillation*

History and Examination. — An Irish American housewife of fifty-four had had, when first seen April 21, 1925, a goitre for four years and thyrotoxic symptoms and exophthalmos for three months. There had been marked and rapid loss of weight and considerable dyspnœa and palpitation on effort during that time. The exophthalmos was of moderate degree only. The thyroid swelling was chiefly in the region of the isthmus where a mass the size of a walnut was felt. There was a loud bruit over the entire gland. The heart was enlarged to percussion with a systolic murmur at the apex. The blood pressure averaged 145/75.

Management. — The median lump was taken to be cystic, but otherwise the case seemed to be one of ordinary Graves' disease. The metabolism fell from plus 80 per cent. to plus 39 per cent. in three days on rest in bed; it is to be presumed therefore that the first at least was not truly basal.

On April 24, 1925, three days after entering the ward, her pulse suddenly became totally irregular actually while being palpated, and remained so for less than twenty-four hours. Electrocardiogram showed auricular fibrillation. There were no important subjective symptoms coincident with these changes in rhythm.

She was placed on Lugol's solution 2 c.c. (30 minims) per day on April 26, 1925, and on April 27, 1925 a test dose of 0.2 gm. (3 grains) of quinidine sulphate was given. No untoward effects resulted from the latter and she was therefore placed on daily doses of 0.4 gm. (6 grains) of quinidine sulphate. The basal metabolism on May 6, 1925 had dropped

to plus 22 per cent. and on May 13, 1925 a subtotal thyroidectomy was done under gas and oxygen. The gland was rather adherent and the portion removed showed some cystic degeneration. The histology of the remainder of the gland, however, was that of follicular hyperplasia.

She stood the operation well, but the second night after had another paroxysm of fibrillation lasting a few hours only, although she was taking quinidine at the time. This drug was continued for two years during

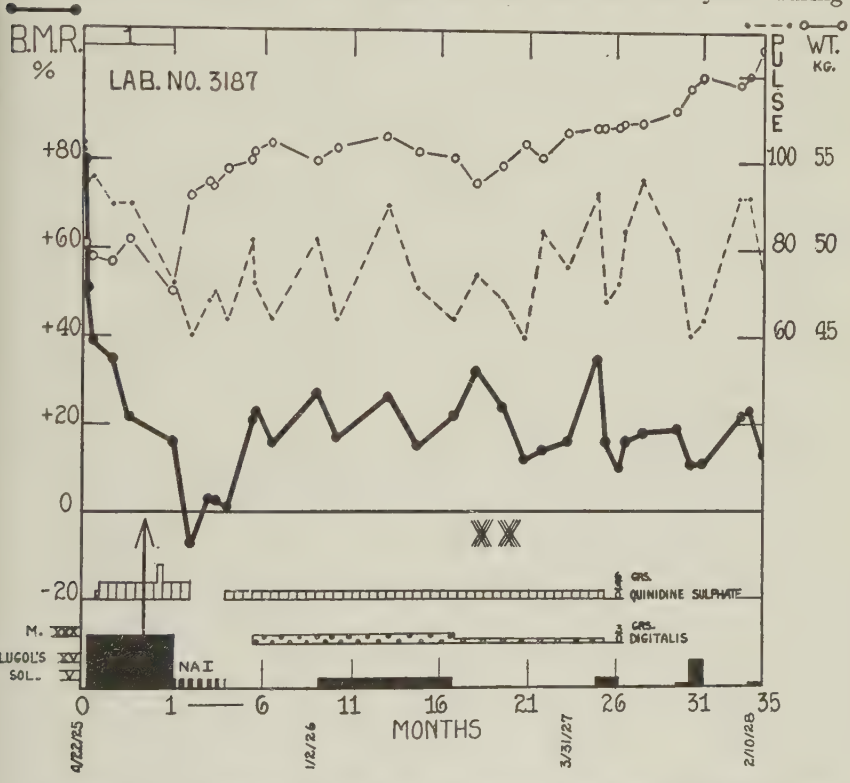

FIGURE 39. *Exophthalmic Goitre with Paroxysmal Auricular Fibrillation (Case No. 3187).*

which time no further fibrillation was observed. For mild signs of congestive heart failure digitalis was given as well during most of this time (see Fig. 39). In the spring of 1928 she was nearly symptom-free with no medication. Three short courses of iodine were given to see whether the metabolism would be depressed. It was slightly in each instance and the patient thought each time that she noted some increased feeling of well-being.

CASE 657. *Exophthalmic Goitre with a Variety of Cardiac Complications Including Permanent Auricular Fibrillation*

History. — A married American railway man of forty-three first came to the hospital on June 21, 1920 with a story of typical symptoms of Graves' disease for four months. Before that he had "enjoyed splendid health for thirty years". He had had severe diphtheria at the age of ten at which time he is said to have injured his heart by getting out of bed too soon, and in consequence his activity was restricted for about a year. At eleven he had "typhoid pneumonia" at which time his heart was again strained necessitating five months' rest. Since then, however, until the present illness his health had been perfect. He had never had any of the rheumatic group of infections and denied venereal disease. He had been married twelve years but his wife had had no pregnancies. No factor which might have precipitated the thyrotoxicosis was discovered.

Examination. — This showed a powerfully built and fairly nourished man with staring expression, slight exophthalmos, lid lag, and wide aperture. There was a moderate sized bilateral soft goitre, larger on the right with bruit on each side. The skin was warm and moist. The color of the skin and mucous membranes was normal. There was a fine tremor of the fingers. The heart measurements were 10 cm. to the left, 3 cm. to the right of midline, the supracardiac dullness was 7 cm. The sounds were rapid and totally irregular; a short, rough systolic murmur was heard at the apex. There was no œdema. The urine and blood were not remarkable. The blood pressure was 135/80, pulse rate 120 at the apex, 90 at the wrist, the basal metabolism +33 per cent., and the electrocardiogram showed auricular fibrillation.

Management. — There seemed little doubt but that he had Graves' disease of not more than moderate severity. The condition of the heart seemed hardly consistent with simple thyroid heart disease. The possibility of an organic mitral lesion was strongly entertained.

Treatment by X-ray was decided upon. He was kept at rest in the hospital and discharged on July 7, 1920 to continue X-ray as an outpatient.

In the fall (October 6, 1920) he was much better. He had then had eight X-ray treatments and had been at half-time work for a month. The eye signs were less, the thyroid smaller, the bruit and all the thyrotoxic symptoms gone, the hands cold and dry, but the heart was still fibrillating. Furthermore, the basal metabolism was still somewhat elevated and the pulse was 100. He was therefore digitalized.

On December 1, 1920 he was symptomatically well and highly

satisfied with his progress, but still had a basal metabolism of +20 per cent. The pulse under digitalis had dropped to 74.

On January 6, 1921, it was decided to continue digitalis indefinitely and allow him to go back to full work.

He was seen again on October 21, 1921. He reported that he had been well and working in the interval. He had changed his job to that of painter and paper hanger. He had continued on digitalis and progressed satisfactorily under its influence on 0.1 gm. ($1\frac{1}{2}$ gr.) per day. Pulse was 83. There was slight exophthalmos and slightest possible thyroid fullness, but very little else suggesting Graves' disease. There was some dyspnœa on effort and he was beginning to be troubled with twinges of precordial pain. The basal metabolic rate was +41 per cent. The heart continued to fibrillate.

From October 29, 1921 to November 9, 1921 he was in the hospital for a second time. During this time a total of 22.5 gm. (336 grains) of quinidine sulphate was given in the hope of stopping the fibrillation, but it did not do so. The basal metabolic rate remained elevated, +34 per cent. on November 5, 1921.

In spite of the heart condition he continued at work and had but few symptoms. On May 8, 1923 the basal metabolic rate was +13 per cent., the pulse 62. On March 21, 1925 he reported himself better than ever. He had been working regularly at painting and paper hanging. Since his previous visit there were no important symptoms, and the only relic of the Graves' disease was slight exophthalmos. The basal metabolic rate was −5 per cent. and the pulse 52. He had gained 10 kg. The heart was still fibrillating and his digitalis ration had been kept up.

In January, 1926 he was not so well and was admitted for the third time to the hospital (January 9 to January 16, 1926). He had developed some headache for which a cause was not found, and also was exhibiting a subnormal metabolic rate. His heart was still fibrillating and he was still taking his digitalis ration. The pulse rate at this time was below normal, sometimes down to 45 at the apex. An X-ray showed widening of both heart and aorta. Syphilitic aortitis was suggested. He was started on 0.2 gm. (3 gr.) thyroid per day.

On this he seemed to get stronger, his headache stopped and on March 23, 1926 his basal metabolic rate was +7 per cent. and his pulse 68. He had only lost 1 kg. body weight. However, the thyroid was kept up for ten months, and then stopped because at that time he was having more dyspnœa and frequent attacks of precordial pain. These continued after thyroid was omitted so that on January 28, 1927 it was necessary to admit him to the hospital for the fourth time. On this

occasion he was clearly gravely ill. The second night he had attacks of angina pectoris, responding to nitroglycerine at first, but later requiring morphia. The lungs showed definite evidence of congestion but there was no œdema elsewhere. The heart was enlarged, the measurements being essentially as at the first entry, over six years before, 9.3 cm. to the left, 2.5 cm. to the right, supracardiac dullness 7 cm. The pulse was slow, weak, and absolutely irregular. The blood pressure was 150/100. Electrocardiogram showed enlargement of the heart and the aorta. Two Wassermanns and a Kahn test were negative. Of Graves' disease there was practically no remnant. The basal metabolic rate was −11 per cent.

After venesection and three weeks' rest in bed he improved somewhat and was discharged relieved. The cardiac condition was regarded as most probably arteriosclerotic with coronary involvement and conduction defect. Syphilis was considered unlikely.

Comment. — This case is presented as an instance of Graves' disease, rather mild, in a subject with independent heart disease, by no means an uncommon combination. Had the cardiac condition been purely thyroid we should hardly have had the subsequent developments after the Graves' disease was passed. It emphasizes the need of suspecting independent heart disease in any patient with exophthalmic goitre when the subsidence of the latter is not followed by the disappearance of cardiac phenomena. It is also of interest that the heart lesion, even with permanent fibrillation, neither aggravated nor prolonged the course of the Graves' disease. Digitalis was essential in this case, but as a means of controlling the rate of the fibrillating heart per se, not in any way directed toward a thyrotoxic condition of the heart. The low metabolism which the patient exhibited from time to time was very likely natural to him, not in any way the result of hypothyroidism.

Diabetes Mellitus

Reasoning nearly identical with that applied to heart disease properly can be applied to the management of diabetes complicating exophthalmic goiter. Just as the strain should be removed from the heart through prompt abolition of the hypermetabolism, so should it be from the pancreas in diabetes. The thyrotoxicosis can be abolished by operation in an iodine remission, and the diabetes then treated in the usual manner.

Fitz[64] in 1921 and Wilder[65] in 1926 both have reported cases of concurrent thyrotoxicosis and diabetes mellitus. That these diseases occur occasionally together is clear, but that there is any causal relation between them is doubtful. Wilder found diabetes in 0.6 per cent. of all cases of exophthalmic goitre. This coexistence is probably accidental. Nevertheless the combination is very important to recognize, for the effect of thyrotoxicosis on diabetes is profound. The sugar tolerance in diabetes is greatly lowered by the development of hyperthyroidism, just as by infection, and a mild diabetes is fanned into a very severe one with an early onset of coma. Under these circumstances the coma may mask the signs of hyperthyroidism. The effectiveness of insulin Wilder finds is less when hyperthyroidism is present, and increases as metabolism drops under iodine. The diabetic exophthalmic goitre patient, therefore, goes into coma easily and requires large amounts of insulin, but at the same time more readily develops hypoglycemia when the dose of the latter is too large. Thyroidectomy therefore should not be long delayed, but preparations for it carried out with great care.

CASE NO. 4016. *Exophthalmic Goitre, Diabetes Mellitus and Auricular Fibrillation*

History and Examination. — A married Nova Scotian salesman of forty-four began to have typical manifestations of Graves' disease four years before he was first seen by us on June 2, 1926. After persisting for two years his symptoms improved spontaneously, but five months before entry to the Massachusetts General Hospital he developed polydypsia, polyuria and polyphagia, and at that time his local physician discovered sugar in the urine. He likewise, during the last three or four months, had had dyspnœa on slight effort and on several occasions attacks of severe dyspnœa at night.

Two months before entering the Massachusetts General Hospital he had been studied in another Boston hospital and the doctor who saw him there reported that he presented the picture of severe thyrotoxicosis with

basal metabolism of plus 100 per cent. and with 5 per cent. of sugar in the urine. In spite of strict diet restriction and large doses of insulin no impression could be made on this glycosuria. He refused further treatment and was discharged with instructions to take insulin and iodine; the latter was taken, the former not. Nevertheless on the iodine alone he apparently improved considerably.

Our examination on June 2, 1926 showed marked exophthalmos and lid lag, an enlarged symmetrical but nodular thyroid with bruit over the right half, profuse sweating, and moderate tremor. The heart was not noticeably enlarged but was fibrillating. There was no œdema. The metabolism was plus 49 per cent. and sugar was present in the urine. Acetone bodies were absent. Blood sugar was 204 mg. per 100 c.c.

Management.— A diagnosis of exophthalmic goitre (probably with adenomata as well), diabetes mellitus, and thyroid heart disease with auricular fibrillation was made. The evident marked improvement in his thyrotoxicosis was believed fairly attributable to the iodine he had taken. The indication for prompt operative treatment was believed absolute on two accounts, the diabetes and the cardiac situation.

He was placed upon Lugol's solution, 4 c.c. (60 minims) per day, on which in nine days his metabolism showed merely the insignificant drop to plus 40 per cent. probably because he already had a full iodine effect at entry.

He was given a diet of carbohydrate 75 gm., protein 75 gm. and fat 135 gm., yielding 1815 calories, and on this without insulin he became sugar-free in a week, although the blood sugar remained at 194. At no time did he show ketosis.

On June 15, 1926 a subtotal thyroidectomy was done under ethylene. The tissue removed showed the usual follicular hyperplasia.

He stood the operation very well, and was kept on the same diet with insulin in diminishing doses, 110 units at the start, for the first week after operation only. He showed glycosuria at no time and the blood sugar fell to 100 on one occasion and 122 three days after insulin was omitted.

Lugol's solution was kept up for twelve days postoperatively in dosage of sixty drops a day, then reduced to thirty. The metabolism two weeks after operation was minus 5 per cent., pulse 72. Digitalis was not required at any time. Nine days after operation, as the fibrillation had continued, a course of quinidine sulphate was begun. After 2 gm. (30 grains) in twenty-four hours normal rhythm was restored. Twenty grains (1.3 gm.) were given the second day, 9 grains (0.6 gm.) the third and fourth, then he was placed on a daily dose of 3 grains (0.2 gm.), and discharged on June 29, 1926.

He was followed from that time on and showed no return of thyrotoxicosis symptomatically. On October 7, 1926 the Lugol's solution was reduced to five drops a day and since there had been no recurrence of fibrillation, quinidine was omitted. The basal metabolism was minus 11 per cent. the pulse 64. His weight had increased from 55.7 kg. before operation to 62.7 kg. His diet was worked up to carbohydrate 117, protein 96, fat 218, without insulin and without glycosuria.

Comment. — This case illustrated well two important complications of Graves' disease, complications which increase the indication for thyroidectomy, in fact which make early operative treatment imperative — cardiac disturbance and diabetes. That the thyrotoxic status aggravates both these, there can be no doubt. When first seen at the clinic he first attended, this patient presented the picture of severe thyrotoxicosis and severe diabetes. The temporary relief of the former by iodine was attended by marked improvement in the diabetes. This ground thus gained was permanently held by the subtotal thyroidectomy. From a severe diabetic, with the abolition of his Graves' disease he became a mild one. The cardiac complication is of less importance, being merely the commonly encountered change in rhythm without other evidence of organic cardiac disease and no congestive failure. Often fibrillation disappears spontaneously after operation. It might have in this case eventually, but it is interesting that it promptly stopped with large doses of quinidine and did not recur on small. The use of quinidine in this way is often valuable.

A rare complication requiring treatment is illustrated by the following case.

Case No. 1988. *Exophthalmic Goitre in a Woman with Chronic Purpura Hæmorrhagica*

History and Examination. — An Irish American housewife, mother of four healthy children, was in the hospital for a week in May, 1923 for a hæmorrhagic tendency which study proved to be true chronic thrombopenia.

It had begun at the age of three with frequent severe nose bleeds and purpuric spots which continued until the age of eighteen, when her first pregnancy occurred. Her periods from the time of their first appearance were very profuse. After the pregnancy the nose bleeds stopped for a number of years, but she continued to bruise easily. There was metrorrhagia for several weeks after each pregnancy and for ten years slight

bleeding from her gums. The spleen at this time was readily palpable and tender. Her basal metabolism at this time was +24 per cent. but there was no other suggestion of Graves' disease. She was discharged to the Huntington Hospital where a course of X-ray, and later radium, treatment was given over the spleen with considerable improvement in her hæmorrhagic tendency. About this time however she began to develop typical symptoms of Graves' disease and on March 25, 1924 she was admitted a second time on account of this new trouble.

The examination showed definite staring expression, wide aperture and lid lag, moderate, rigid, bilateral goitre with thrill and bruit, and tremor of the fingers. There were also a few purpuric spots and her spleen was palpable as before. Blood showed a great diminution in platelets.

Management. — This patient presented an interesting problem from the point of view of therapy. Which of her diseases should be treated first, and what method should be employed for each? Her purpura seemed not especially active and the Graves' disease quite definitely so. On account of the possibility of bleeding at operation, X-ray therapy for the goitre was decided upon. Iodine was given coincidentally. A series of four X-ray treatments in March, April, and May, 1924, together with iodine brought about a very satisfactory improvement.

In October, 1924, however, the thyrotoxic symptoms recurred while the purpura seemed in abeyance. Because of the good response to the first course of X-ray it was determined to try it again. This was done in November and December, 1924, and January, 1925. There was again marked improvement in symptoms but not complete disappearance.

Through the summer of 1925 she remained somewhat toxic, but in the autumn there was a distinct improvement. She was last seen April 6, 1926 and then was symptomatically over her Graves' disease, and her purpura was still in abeyance.

Comment. — We have here an exceedingly rare complication of exophthalmic goitre. It represents, however, some of the difficulties that may arise in planning the treatment of that disease. Operation on the thyroid was thought risky and a moderately good result was secured with X-ray. It is of interest, too, that her purpura hæmorrhagica was not aggravated by the thyrotoxicosis; in fact it was for the most part in abeyance both during and after the latter had run its course.

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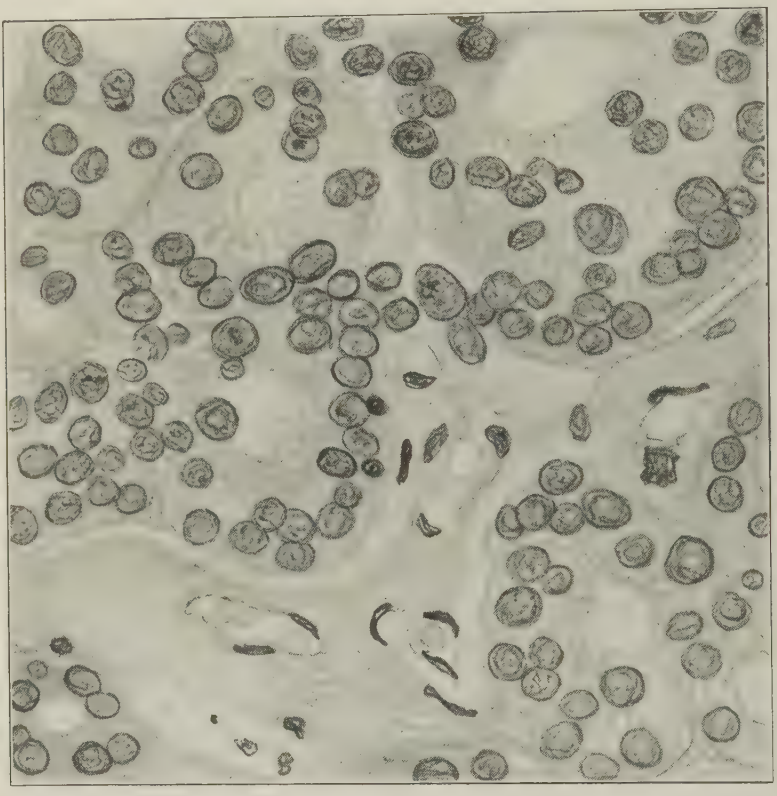

FIGURE 40. *Fœtal Adenoma of the Thyroid.* High power camera lucida drawing. Note the small but smoothly outlined follicles and the absence of colloid.

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CHAPTER VII

ADENOMATOUS GOITRE

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INTRODUCTION

Benign tumors, or tumor-like nodules of the thyroid parenchyma are very common. These tumors as a group are definitely encapsulated, the capsule consisting in large measure of the stroma of compressed gland tissue surrounding them, in which persisting alveoli may be detected under the microscope. They may appear as single or multiple discrete nodules developing within the thyroid capsule, surrounded by or displacing normal thyroid tissue, or at times replacing practically the whole gland. Anatomically they may be made up of follicles of the adult or of the fœtal type, in the latter case consisting of small closely packed alveoli containing little or no colloid; this distinction can be made only on pathologic examination. Certain instances of colloid goitre in which the masses of follicles distended by colloid, whether localized in part of the gland or distributed through it, are circumscribed by fibrous tissue caus-

ing a nodular rather than a diffuse enlargement, are included by us under the general heading of adenomatous goitre, since both in clinical diagnosis and in the indications for treatment they are not to be distinguished from a more definitely adenomatous type. These nodules in the gland are sometimes described as colloid goitres, sometimes as adenomatous, but are commonly referred to surgically as "colloid adenomata". Therefore in this group of nodular goitres there are some which are clearly not neoplastic; others, particularly among those showing a structure resembling the fœtal thyroid, may be considered true tumors. In spite of this consideration we speak of an encapsulated nodule of thyroid tissue as an adenoma, including in this term those made up of colloid follicles with slight evidence of hyperplasia. The nodules in adenomatous goitre are prone to degenerative changes, necrosis, hæmorrhage and calcification. The numerous instances of cyst formation, often described as cyst-adenomata, usually are secondary to this cause. Occasionally there may be evidence of a new formation of follicles throughout the gland without encapsulation, a condition to which the term adenomatosis has been applied[1, 2, 3]. The histologic picture of adenomatous goitre therefore varies, not only between different glands, but between different parts of the same gland.

The actual microscopic appearance the gland presented, in the absence of malignancy, is of relatively slight clinical importance. From a practical point of view the important clinical classification is functional. Thus adenomatous goitre may be associated with a normal or reduced function, or it may be associated with hyperfunction and the constitutional disturbance associated with high metabolism. While typical instances of these two conditions are distinct, they merge into each other,

so that in certain cases it may be doubtful whether or not toxæmia exists. The diagnosis of adenomatous goitre with hyperfunction is clinical rather than pathologic, because there is no generally agreed upon morphologic evidence of increased functional activity in adenomatous goitre.

The cause of these tumors is known no more than is that of any other tumor. We do know that there is a relation to endemic goitre and iodine lack, because adenomatous goitre is abundant in endemic goitre regions, particularly in persons who have suffered previously from diffuse colloid goitre. Its incidence furthermore is cut down by goitre prophylaxis. Nevertheless, this is far from the whole story, for many adenomatous goitres are seen in persons who never have resided in goitrous regions, and in whom no detectable goitre has ever existed.

The variation in occurrence of adenomatous goitre may be seen in relation to exophthalmic goitre, which appears to have no geographic variation in distribution. Thus in our clinic which draws chiefly from a non-goitrous district, the ratio of exophthalmic to adenomatous goitre coming to surgical treatment is about 1:1, and of the latter about thirty per cent. show some evidence of hyperthyroidism. This may be contrasted with de Quervain's[4] statement that in Switzerland exophthalmic goitre forms only about four to five per cent. of goitres among the indigenous population. Pemberton[5] states that at the Mayo Clinic during 1924, of 1886 goitres operated on, 741 were exophthalmic goitre and 1145 were adenomatous. Of the latter 368 were classed as adenomatous goitre with hyperthyroidism.

Diagnosis

Diagnosis is concerned with two questions, local and constitutional; in the first place, with the recognition of an adeno-

matous condition in the thyroid by inspection and palpation, and in the second, with determination of the presence or absence of symptoms of hyperthyroidism.

The pathognomonic sign is a goitre with a nodular consistency, usually present as an asymmetrical enlargement. Although this sign is not invariably present, the diagnosis can be made with certainty only when it is. Single nodules may vary from a size barely palpable to that of an orange, and when small, usually may be distinguished from the remainder of the thyroid lobe by their firmer consistency. They are rounded, smooth, commonly tense and elastic, but may be fluctuant, and do not approach the stony hardness of some malignant tumors except when calcified. Frequently multiple nodules may be palpated, sometimes discrete, sometimes grouped together, at times replacing all vestige of normal thyroid tissue. Adenomatous nodules may be an unexpected finding in large or firm goitres removed at operation. When marked cyst formation has occurred, the goitre may attain great size, and individual nodules may be lost to palpation in the total mass. The finding of a nodular goitre, provided malignant disease can be ruled out, or the presence of large goitres with cyst formation, justifies the clinical diagnosis of adenomatous goitre.

The clinical diagnosis further should include a statement as to whether hyperthyroidism coexists, for it is believed that these tumors may give rise to thyroid hyperfunction, and it is at least certain that there may be hyperfunction which sometimes develops in persons in whom they occur. For this reason we use the terms toxic and non-toxic to designate the presence or absence of hyperfunction in adenomatous goitre. It was Plummer[6] who separated adenomatous goitre with hyperfunction as an entity distinct from Graves' disease. There is much to recom-

mend his classification, though it has by no means gone unchallenged[7, 8]. Those who take exception to it for the most part admit the existence of adenomata in certain thyrotoxic persons, but doubt whether they have any particular significance. Toxic goitre is toxic goitre, they would say, regardless of whether adenomata are present or not. All toxic goitre should come under one category, Graves' disease, and any attempt to separate two entities is unwarranted.

Differential Diagnosis

The differential diagnosis, therefore, from the physiologic point of view, is largely from exophthalmic goitre and all the conditions which simulate hyperthyroidism. From the anatomic side it is chiefly from malignant tumors of the thyroid. Confronted with a nodular goitre we think, first, is it malignant or benign; second, is it producing hyperthyroidism? Sometimes in adenomatous goitre with hyperfunction the symptomatology may suggest chiefly cardiac insufficiency, and we may be called upon to distinguish between heart disease of purely thyroid origin and some other type of heart lesion.

The differentiation between adenomatous and malignant goitre is of vital importance, but unfortunately can not be made with certainty. For an absolute diagnosis we must depend on the evidence of invasion of surrounding tissues with consequent fixation of the tumor. But at this stage the growth is beyond the hope of cure in the vast majority of cases. We must appreciate, therefore, that carcinoma of the thyroid arises most frequently in adenomatous goitres, and look for any suggestive evidence of malignant change, such as increase in the rate of growth or a firmer or harder consistency than usual. The chief hope of cure lies in surgical removal before the growth

has broken through the capsule of an adenoma. The best results from operation, therefore, come from removal of a gland supposed to be adenomatous before the diagnosis of malignancy can be made clinically. While most cases of carcinoma of the thyroid show a metabolism within normal limits, at times the rate may be elevated; therefore, the presence of hyperthyroidism is no assurance that malignancy does not exist. For a further discussion of the subject, see Chapter IX.

Adenomatous goitres on account of their size and irregular growth are likely to produce conspicuous deformities and symptoms due to pressure either in the neck or in the thorax. In the latter case, particularly if no enlargement of the neck is present, we have to distinguish between pressure caused by an intrathoracic goitre and that by some totally different type of tumor.

The differential diagnosis between adenomatous goitre with hyperthyroidism and Graves' disease depends on the history of the case, the character of the goitre, and the absence of some of the symptoms characteristic of the latter disease. In adenomatous goitre with hyperthyroidism ("toxic adenoma") there is likely to be a history of long-standing goitre. On this account the incidence of the symptoms of toxæmia are likely to occur at a greater average age than in Graves' disease. Characteristically the onset of toxæmia in adenomatous goitre is very gradual, and the patient, even though obviously thyrotoxic and conscious of failure in health, may be unable to set any time for the beginning of the disability. This insidious development is in sharp contrast to many cases of Graves' disease in which the march of events is steadily toward a fully developed toxæmia, and in which the date of onset of the changes from health, emotional instability, loss of weight and strength and tachycardia, although

varying in order of development, can be placed with approximate accuracy. Particular weight for the diagnosis of Graves' disease is given by the development of the goitre at approximately the same time as the nervous and constitutional symptoms.

The type of the goitre differs in the two conditions. In adenomatous goitre it has characteristics previously described, being nodular, asymmetrical, or of varying consistency, prone to degenerative changes, while in Graves' disease it is diffusely and symmetrically enlarged, firm and uniform in consistency, and shows in exaggerated fashion the typical shape of the gland. A bruit and thrill is more constantly associated with Graves' disease.

In the symptoms and signs there are also differences which consist in the absence in adenomatous goitre with hyperthyroidism of some of the features peculiar to Graves' disease. The chief of these is the exophthalmos and associated eye signs, which are rarely present in adenomatous goitre. In this condition, too, the nervous manifestations are much less severe, and patients lack the intense nervousness and psychic instability of Graves' disease. While in Graves' disease the metabolic rate may be predicted with fair accuracy, based on easily obtained evidences of the disease, in adenomatous goitre with hyperthyroidism this is more difficult on account of less obvious nervous disturbances, vasodilatation, tremor and sweating, so that at times one is surprised at the extent of increase above normal. It is true, however, that the higher rates of metabolism, as we see them, are more common in Graves' disease.

While it is possible to block out two main groups of cases in which the history, the character of the goitre and the symptomatology are in definite contrast, it must be recognized that there are intermediate cases, in which classification into one

group or the other may be extremely hard. The type of case, which causes most difficulty in this locality, shows a rather gradual onset of toxæmia at or beyond middle life without pre-existing goitre and has slight or absent eye signs. In such cases the thyroid is only moderately enlarged, and while it may feel nodular in consistency on account of irregularities in shape, it shows on section a homogeneous surface, and on microscopic examination the hyperplasia of Graves' disease. The presence of adenomatous nodules in the thyroid does not prevent the development of the diffuse changes associated with exophthalmic goitre. We may feel these nodules in the gland and attribute symptoms to them, while the actual cause is the changes which have occurred in the rest of the gland tissue about the nodules. The matter of accurate diagnosis in these conditions is not of great moment. The interests of the patient are best served both in the preliminary treatment and in the operation, if we consider that they have exophthalmic goitre, and in the first instance saturate them with iodine, and in the second, remove all thyroid tissue except that necessary for normal function.

In the differentiation between adenomatous goitre with and without toxicity, principal weight must be given to the metabolism determination. In early cases of mild degree, a persistent elevation of metabolism with slight increase of pulse rate may be the only evidence of hyperfunction. Conspicuous complaints of nervousness, excitability, trembling, or increased sweating, are likely to be absent. Instead, patients may complain of shortness of breath, loss of weight and strength, or rapid and perhaps irregular heart action. On account of the gradual onset the patient may become so accustomed to many of these disabilities that the principal symptoms may be of cardiac origin. Thus these patients may be presented as in-

stances of cardiac disease with fibrillation, paroxysmal or continuous, or even with evidence of congestive failure. This aspect of the case may so overshadow the presence of goitre that a causal relation between the two is even doubtful. Diagnosis depends on the exclusion of other known varieties of cardiac lesion, rheumatic, syphilitic, hypertensive, or arteriosclerotic. Since the metabolism may be elevated in cardiac failure, this test can not be relied upon entirely. However, if after complete study of the case, including electrocardiography and X-ray examination, it seems possible that the thyroid bears relation to the cardiac condition, surgical removal of the goitre is desirable. Occasionally striking exceptions to the gradual development of hyperthyroidism will be found.

Adenomata presumably manufacture thyroxin as does other thyroid tissue, but in the beginning at least this function is ordered by the mechanism governing that of the entire gland in such a manner that total hormone manufacture meets but does not exceed normal requirements. In a certain number of cases it appears that after adenomata have existed for a while, this control is lost, and for some reason quite unknown, the tumors commence manufacturing thyroxin in excess of body requirements. In other words they begin to hyperfunction and produce hyperthyroidism and its symptoms. The transformation from the non-toxic to the toxic stage of adenomatous goitre is usually gradual and why it takes place is utterly unknown. In a few instances it seems to follow the taking of iodine, and there is a noteworthy number of writers who decry the wholesale use of iodine for goitre prevention on the score that it will activate or render toxic a certain number of simple adenomatous goitres[9]. Then in former days, it also will be recalled, Theodor Kocher[10] believed that many simple goitres were rendered toxic

by iodine. He applied the term "Jodbasedow" to such cases, and was largely responsible for the ill repute that iodine possessed for years in the treatment of exophthalmic goitre. Plummer[11] has gone on record as believing that iodine will activate simple adenomatous goitre, and we have seen a few cases ourselves that strongly suggest this.

Activation may also come about through underactivity of the rest of the gland. Plummer[12] cites six cases in which after extensive thyroidectomy for colloid goitre, in the remaining tissue, apparently to meet a shortage of available gland parenchyma, there developed adenomata which apparently through their activity met the need. We have seen a similar case. Nevertheless in the majority of instances the cause of transformation to the hyperactive state is obscure.

Certain other iodine relationships are of interest. Although, as we have seen, there is some reason to believe that iodine may render simple adenomata toxic, it is clear that once hyperthyroidism has supervened, iodine does not make it more intense. Whether, on the contrary, it brings about a remission, as in exophthalmic goitre, is a matter of lively dispute and even brings up the problem of whether there actually is any such condition as hyperfunctioning adenomatous goitre. Plummer[11] in separating the two types of thyrotoxic disease lays great weight on the peculiar Graves' manifestations which he claims are not seen in hyperfunctioning adenomatous goitre. He also stresses the difference in onset and the pre-existence of goitre to toxic symptoms in the latter condition. Furthermore he claims that the simple removal of encapsulated adenomata, without disturbance to the rest of the gland, often permanently abolishes the hyperthyroidism. From this he infers that the adenomata are solely responsible. Our experiences lead us to a similar conclusion.

The reaction to iodine is another point on which differentiation may rest. Were Plummer correct that the effect of this agent in exophthalmic goitre is solely to convert a perverted into a normal type of thyroxin production, and if in adenomatous goitre with hyperfunction we are dealing solely with an excess of a normal product, then iodine should be without effect, unless perchance it exercises some control over rate of secretion. That it may do this last is suggested by the "Jodbasedow" cases. But to assume that under certain circumstances it activates and in others retards the action of thyroid cells, is to enter the field of pure speculation.

Setting theory aside we may seek facts, but here we are balked by the matter of diagnosis. Some writers strongly testify that iodine remissions are quite as readily produced in adenomatous goitre with hyperfunction as in exophthalmic[8], and use this as an argument that the two conditions are the same. Others would deny that any of the cases so reacting had uncomplicated adenomatous goitre. The fact that iodine remission occurred would, they claim, indicate that all such cases were exophthalmic.

We have seen several cases conforming to the requirements of Plummer's disease which did respond quite typically to iodine. It is conceivable that "adenomatous" toxic goitre is a stage of Graves' disease and that the nodules represent involutional changes which might be expected in the more chronic forms of the disease. We have seen "adenomatous" goitre patients with the characteristic eye-signs, and they do not differ from the usual cases of Graves' disease in any important respect except for the nodular character of their thyroid glands, their longer duration and their higher incidence in the older age groups.

Clinical Course

The clinical course of thyroid adenomata is that of very slow growth extending over many years. When a patient is examined at intervals of six to twelve months, it may be uncertain whether any growth has taken place. At times the degenerative processes may lead to actual diminution in size. The course, after hyperfunction has begun, has been indicated sufficiently in the discussion of diagnosis. Whether or not it is occasionally a self-limited disease with eventual restoration of a normal metabolic rate, such as sometimes occurs in Graves' disease, we are unable to say. Our impression is, however, that once an adenomatous goitre has begun to function excessively, it continues to do so unless interrupted by some form of destructive treatment.

Precisely what proportion of adenomata ultimately will become toxic is difficult to say. Plummer[12] found that, "only five per cent. of the hyperfunctioning adenomatous goiters coming under observation at the Mayo Clinic" were "in patients under thirty years of age", also that these constituted "about five per cent. of all adenomatous goiters resected in patients under the thirtieth year. Sixty per cent. of all such thyroids, resected in patients after the sixtieth year" were hyperfunctioning. "The average interval between the time the goiter is first noticed and the onset of hyperthyroidism, including only those that hyperfunction before coming under observation, is seventeen and six-tenths years."

In our clinic hyperfunction occurs in about thirty per cent. of adenomatous goitres. It is fair to say, however, that in most of the cases the toxæmia is very mild, and that the group is

much enlarged by the inclusion of patients in whom the principal evidence of toxæmia is a metabolic rate between plus 20 per cent. and plus 30 per cent. Adenomatous goitres with a severe grade of toxæmia are not common in this locality.

An adenomatous goitre becomes productive of symptoms through pressure, through its size and through hyperfunction. We must recognize further that such a goitre, even if productive of no symptoms, is not only potentially a source of trouble for these reasons, but also carries an increased liability to malignancy. Fluctuation in size, which occurs sometimes, may cause anxiety, and often quite a marked hypochondriacal psychoneurosis may be built around one of these glands. Hæmorrhage into a cyst may cause sudden and perhaps alarming enlargement of the goitre and may lead occasionally to acute pressure symptoms. Extreme cystic degeneration may lead to goitres of a colossal size, which are not only unsightly, but a cause of great annoyance. That an adenomatous goitre may produce constitutional symptoms and visceral degeneration in the absence of increase in the metabolic rate has been suggested by Coller[13]. Our impression is that the effect of such a goitre without hyperfunction is purely local. While it is true that patients after removal of thyroid adenomata may gain in weight and are improved in health, we have been unable to convince ourselves that this is due to anything more than relief from pressure and freedom from the anxiety and constant irritation caused by a visible deformity.

Complications

Cardiac

In both Graves' disease and hyperfunctioning adenomatous goitre, the heart has extra work to do. If thyrotoxicosis con-

tinues for long, therefore, hypertrophy may be expected. It seldom is more than moderate in extent. Much debate has taken place as to whether, especially in Graves' disease, there is a direct toxic effect as well. Goodpasture[14] has produced experimentally lesions in rabbits' hearts by thyroid feeding. Whether such an action is important in the human being remains in doubt. The facts are that in both types of thyrotoxicosis the heart, after the toxic state has been abolished, shows a remarkable recuperative power.

In general, cardiac manifestations are more marked in the adenomatous type. This is probably attributable to the facts that the patients are older as a rule and hence more sclerotic or hypertensive, and that the duration of the hyperthyroid state is usually longer. In the beginning of hyperfunction the intensity of hyperthyroidism may be mild for a period of years even, and the symptoms not sufficiently marked to cause annoyance, yet all the time the heart is under some extra load.

The cardiac symptoms are not infrequently the first in this type of disease. Palpitation is often pronounced; many cases are met in which it is paroxysmal. When so, it is generally due to paroxysmal fibrillation, which is especially common in this form of thyrotoxicosis. Ordinary congestive heart failure is seen, but less frequently than are the disturbances in rhythm. Thyroidectomy, particularly if it is carried out with local anæsthesia, ordinarily is well tolerated in spite of cardiac deficiency. Of course, careful preliminary preparation is essential. If the thyroid is primarily at fault, no other therapeutic procedure can benefit the heart so permanently.

The use of digitalis in either variety of thyrotoxicosis is problematic. When gross cardiac insufficiency exists it must be given. For fibrillation without definite insufficiency it is of

FIGURE 41 *Intrathoracic Goitre.*

Facing page 267.

very doubtful value. Some observers believe that under such circumstances actually it may be harmful, or at least that operative mortality is higher when it is used in the preparation for operation than when it is not.

In those cases giving a story of, or known to have had paroxysmal fibrillation, quinidine may be given prophylactically before operation (0.3 gm. (5 gr.) once daily for a week before operation and two weeks after). For those already fibrillating and who do not regain normal rhythm within two weeks after operation, intensive quinidine therapy as outlined in Chapter VI should be employed.

Pressure Symptoms

Pressure symptoms are produced more commonly by adenomatous goitre than by any other type. This is due in part to their irregular and nodular character, in part to the large size attained, but chiefly because they are prone to extend downward. Pressure occurs because the goitre is confined, either by firm overlying muscles or by its fibrous attachments, or more commonly, by the unyielding bony ring of the superior thoracic aperture. Goitres which produce a conspicuous deformity in the neck with stretching of the overlying muscles tend to fall forward and downward, causing traction rather than pressure.

Pressure is commonly caused, therefore, by extension of the goitre to a greater or less degree into the superior mediastinum [15, 16, 17, 18]. These goitres may be classed as partially or completely intrathoracic, or according to position, as substernal or subclavicular. While exceptionally the enlargement of aberrant thyroid tissue may lead to an intrathoracic goitre, the common origin is in the neck and extension downward is

secondary. Although it is possible for a diffuse colloid goitre, or very rarely for a hyperplastic goitre, to progress downward, the great majority of intrathoracic goitres are adenomatous or nodular colloid goitres and consequently properly are discussed in this section. As we have pointed out, there is no bar to descent in this direction except the attachments of the thyroid to the trachea and larynx, while the pressure of overlying muscles, gravity, the movements of swallowing, and thoracic aspiration, all encourage a downward advance. Partially intrathoracic goitres are naturally commoner than completely intrathoracic goitres, and the incidence of both varies in different clinics. It is fair to say that about ten to fifteen per cent. of simple goitres show some extension into the mediastinum at the time when surgery is undertaken, while about one per cent. are completely intrathoracic. The condition is commoner in women than in men and more frequent with advancing years.

The most usual *symptoms* are dyspnœa and a sense of substernal pressure. An irritative cough is common, and choking spells occur occasionally. Headache frequently is complained of, due presumably to venous congestion. Difficulty in swallowing sometimes is present. Changes in the voice, which may vary from a slight hoarseness to aphonia, are not unusual and are associated with impairment of the recurrent laryngeal nerves. Exceptionally a severe respiratory stridor is present. These symptoms are likely to be gradual in development and progress slowly, sometimes over a number of years. Acute intensification of the symptoms may be associated with hæmorrhage into the goitre, while a rapid progression is suggestive of malignancy. Toxæmia may originate in goitres in this as in any other situation, so that constitutional disturbances from this cause may be added to the picture.

Diagnosis is relatively easy in cases where there is a palpable goitre in the neck, or when there has been a history of goitre which became lower in position and subsequently disappeared. Where neither of these conditions exist, an intrathoracic goitre is overlooked readily, and the patient treated for asthma or some other pulmonary disease, or for cardiac failure. At times attention may be so taken up with a definite goitre in the neck that a mediastinal extension is not found even at operation. Although the presence of goitre may not be demonstrated, some type of mediastinal tumor usually is suggested by the symptoms, and frequently by dilatation of the superficial veins of the neck or arms with the formation of collateral channels, or perhaps by increased supracardiac dullness.

When a goitre is present, if the lower margin of both lobes can be felt clearly on swallowing, intrathoracic goitre is unlikely, but if the lobe shades off so that it is lost to palpation in the root of the neck, such an extension is probable. The top of the goitre may be felt in the sternal notch, sometimes only when it rises on coughing. A lateral deviation of the trachea, unexplained by the tumor in the neck, is very suggestive evidence of a mediastinal lobe. In differential diagnosis other forms of mediastinal tumor should be considered: aneurysm, thymic enlargement, Hodgkin's disease, or non-thyroid malignancy. The essential diagnostic measure is X-ray examination, which should be made as a routine. By this means only may the size and depth of the goitre be determined. Ordinarily the character of the shadow, rounded, well defined, usually making a sharp angle with that of the aorta, points clearly to its source, while displacement of the negative shadow of the trachea may serve further to define the situation of the mass.

Treatment

Adenomatous goitre per se is only treated satisfactorily by surgery. The use of iodine to reduce the size of the goitre is not only often dangerous through the production of toxicity, but ineffective, as it has been in our hands. The choice lies between advising operation and keeping the goitre under observation without treatment. While it is a matter of common experience that patients sometimes tolerate adenomatous goitre for years, perhaps through life, without coming to any harm, the possibilities are so serious that the policy of complete neglect can not be acquiesced in.

Carcinoma when it develops originates in preëxisting adenomata in ninety per cent. of instances[19]. The actual incidence of carcinoma is difficult to determine, but it constitutes from one to two per cent. of thyroid cases coming to surgery. Further, there is the possibility of development of toxic constitutional symptoms. According to Plummer's statistics, three patients out of every five with adenomatous goitre, who live to sixty, will develop hyperthyroidism. While a reasonable regard for prophylaxis suggests the removal of thyroid adenomata, this does not mean that operation invariably should be advised. The therapeutic problem is concerned chiefly with adenomata of small size, particularly in young individuals, since in them the risk of complications is less, while the chance of recurrence due to overlooking small nodules is greater. Thus a tumor, two or three centimeters in diameter, productive of no symptoms in a patient of thirty or younger hardly seems to demand removal, while at forty-five or fifty we should advise it. If such a tumor were situated low in the thyroid where progression into the mediastinum was likely, we should insist on removal more strongly than if high in the lobe.

Definite indications for operation are conspicuous deformity, pressure symptoms of any type, increase in rapidity of growth, or the development of toxæmia. When hyperthyroidism develops, operation is particularly desirable, since cardiac changes are prone to accompany this type of goitre. While the X-ray sometimes reduces toxæmia from this source as well as causing a diminution in the size of the goitre[20], we do not advise it because surgery gives prompt and more certain results.

The results of surgery in adenomatous goitre are dependent on the time at which operation is undertaken. While it is to be expected that indifferent or ignorant individuals will continue to delay in seeking medical advice, there is no reason why patients should drift into a serious condition when this advice is once obtained and followed.

In adenomatous goitre without hyperthyroidism, the late results of operation, as might be expected following removal of a benign tumor causing no constitutional disturbance, are eminently satisfactory. In occasional cases more adenomatous nodules may recur after months or years either from small centers of growth overlooked at operation or from the development of new ones. If they attain sufficient size to be troublesome, they may be removed at a second operation. This course of events is particularly likely to take place in young individuals and is a reason for postponing operation in patients with small adenomata under the age of thirty.

When all parts of the thyroid are the seat of adenomatous change, it is to be expected that the abnormal tissue left occasionally will hypertrophy. Nevertheless it is better to take the chance and leave enough thyroid tissue for function, even if adenomatous, than to remove the whole gland. In adenomatous goitre with hyperthyroidism our impression

agrees with the findings of Judd[21] that the results of surgical removal lead to a more complete constitutional cure than in exophthalmic goitre.

It is desirable to do subtotal thyroidectomy for nodular goitre of all types. In the toxic type it is best to do so in order to avoid persistence or recurrence of the disease. A five year post-operative follow up of 60 cases of non-toxic nodular goitre made in our clinic in 1934 (Hertz) indicated that it was also desirable to do subtotal thyroidectomy in this class of case from the standpoint of recurrence of other nodules. Four cases showed a recurrence of non-toxic nodular goitre in the group of 16 of the 60 cases in which anything short of subtotal thyroidectomy was done. Only one of the 44 cases in which subtotal thyroidectomy was done had a recurrence within the five year period.

Pressure on the sympathetic may give rise to eye-signs. Exophthalmos and Horner's syndrome occur in such cases as indirect mechanical symptoms. Dysphagia indicates an encircling type of goitre, and surgeons should look behind the trachea and œsophagus for thyroid tissue in such cases. Sudden increase in size of a goitre during labor has necessitated emergency thyroidectomy. It is better to operate early in pregnancy, if the goitre enlarges or is of mechanical significance, than to run the risk of an emergency operation later on.

Inability to sleep on either side is a common mechanical symptom and may be caused by a substernal goitre. Hemoptysis has occurred in association with non-toxic nodular goitre of considerable size and may be on the basis of venous interference. Dilatation of the superficial veins may assume rather striking proportions, and undoubtedly the deeper veins are likewise affected.

Intrathoracic goitre may occur deep in the chest as it did in one of our recent cases in which an adenoma was removed from the region of the diaphragm by a chest surgeon.

Anginoid symptoms and dyspnœa simulating cardiac disease may be caused by intrathoracic goitre and be relieved by operation.

When a nodule is removed, and an unsuspected malignancy is found, a prophylactic course of x-ray treatments is worthy of trial, if there has been any evidence that the growth was not entirely localized. But if the entire lesion has been widely resected, it is better to wait for palpable recurrence of tissue before instituting x-ray therapy.

Of eight cancer cases, which were followed up in our clinic, two were found in which previous operations were done many years before for non-toxic nodular goitre, and this small experience is against such operations as an effective prophylaxis against cancer. The removal of single or multiple nodules with the incidental and unexpected finding of true malignancy, however, has occurred often enough to warrant such operations on patients where nodules show any tendency to increase in size under observation.

Illustrative Cases

Case No. 4370. *Adenomatous Goitre with Hyperthyroidism; Onset with Dizziness.*

History. — A graduate nurse of 68, superintendent of a college infirmary, entered the hospital December 3, 1926. Her first symptom had been an attack of dizziness coming on while in church fourteen months before. She had gone out into the vestibule and sat quietly for a time, then walked home. There was no further symptom for seven months, during which time she had worked hard and toward the end of the period grown tired. A second attack of dizziness then occurred, this time

accompanied by a queer feeling in the heart which was rapid and she thinks irregular. She lay down for a couple of hours and all symptoms passed off.

Two months later there was a third attack like the second, but this time with less dizziness and more palpitation. The heart was described as rapid and irregular and "seemed to be turning over". This attack lasted several hours, but the next day she started alone for her vacation, making a train journey and carrying her own suitcase. For a few days she felt well but then within a week had two attacks of severe palpitation and a sensation of heat in the head. The symptoms soon became more continued, and she was put to bed, where she had remained for four months until the time of entry to the hospital. The symptoms were chiefly dizziness, palpitation and tachycardia, together with certain visual disturbances. There were also increased sweating and trembling.

She had had a goitre since the age of 14. It had undergone no change at any time so far as she was aware. After she was put to bed she was given Lugol's solution for ten days, which made her no better, in fact she thought worse. It did not affect the size of the goitre.

Examination. — Examination showed a fairly well nourished and well preserved woman of 68. There was nothing abnormal about the eyes. There was a moderate sized, hard, irregular, bilateral goitre larger on the left, with a bruit on the left side only. There was a definite tremor of the extended fingers. The physical examination in other respects was not remarkable, and the only laboratory finding of importance was the elevated basal metabolism.

Management. — A diagnosis of adenomatous goitre with hyperthyroidism was made, and she was kept in bed for ten days during the last five of which she was given Lugol's solution. There was a slight decline in metabolism and a more marked one in pulse. A subtotal thyroidectomy under ethylene was done. An irregular gland was found showing on section a coarsely lobulated structure composed of spherical encapsulated nodules of various sizes 1 to 3 cm. in diameter, some of which were calcified.

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
Dec. 6, '26	+54	116	53.0	
" 13, '26	+40	100	52.0	
" 14, '26				Subtotal thyroidectomy
" 22, '26	+10	92	51.8	

Histologically the follicles were symmetrical in shape; some were dilated with colloid. Most were of small size and gave the impression of active growth. They were separated for the most part by a loose stroma which contained serum, red cells, colloid, and often areas of degeneration. The epithelium was cuboidal and pale staining. There were no papillary ingrowths.

Convalescence was uneventful and at the time of discharge, January 15, 1927, she was essentially symptom-free. Seen a year later, January 16, 1928, she showed no evidence of thyroid disease or of cardiac damage. She was back at work.

Comment. — The history is very different from that of Graves' disease. The existence of goitre since puberty with the development of toxic symptoms only in old age is highly characteristic of Plummer's type. The onset is interesting. We are inclined to believe that the three attacks were paroxysmal fibrillation. They often occur in this disease and may precede other symptoms. Finally a continued symptomatic hyperthyroidism developed, but lacking many of the cardinal features of Graves' disease.

The scant response to iodine is noteworthy and consistent with our ideas on the malady. Finally the histologic picture, different in all respects from exophthalmic goitre, should be emphasized.

CASE NO. 1681. *Adenomatous Goitre Becoming Hyperactive under Iodine in a Woman with Old Endemic Colloid Goitre.*

History and Examination. — An American housewife of fifty-four, born and raised in Wisconsin, was first seen on October 4, 1922. For twenty-five years or more there had been a diffuse enlargement of the thyroid unproductive of symptoms of any kind. She had borne four children successfully; they were all living and in normal health.

Six months before we saw her, because the goitre had increased slowly in size, she was ordered to take iodine by her family physician for the purpose, she said, of decreasing its size. After a month of such medication she gradually became weak and shaky, and suffered considerably from pounding of the heart and throbbing in the neck. These symptoms increased gradually in intensity and in addition there was dyspnœa, anorexia, insomnia and loss of twenty pounds in weight. Coincident with these symptoms her catamenia stopped. An acne eruption appeared upon the skin and the goitre showed no decrease in size.

She showed signs of weight loss and a marked bilateral enlargement of the thyroid. Both lobes and isthmus were involved, especially the latter.

The surface was irregular and nodular, and a bruit was heard over both superior poles. There were no eye signs whatever, but a marked fine tremor was present. The heart action was violent and the heart slightly enlarged both by physical and X-ray examinations. There were loud, rapid, regular heart sounds with a harsh systolic murmur over the whole precordium. The blood pressure was 175/85. The basal metabolism was plus 46 per cent. and pulse 107 on one occasion, and four days later plus 46 per cent. and 96 respectively.

Management. — A diagnosis of adenomatous goitre with hyperthyroidism was made. On ten days' rest in bed in the hospital she improved somewhat. The basal metabolism dropped to plus 40 per cent. and the pulse to 96. No iodine was given.

On October 18, 1922 a subtotal thyroidectomy was done under gas and oxygen. The goitre was found to consist chiefly of an enlarged right lobe full of adenomatous nodules. Except for a small bit at the upper pole the whole lobe was removed. The left lobe was smaller but also filled with nodules and it too was removed save for a small bit at the upper pole. The portion removed was the size of a grape fruit and showed a lobulated encapsulated tumor. On section it was reddish brown with translucent surface and areas of calcification. Histologically the follicles were dilated with eosin-staining colloid and lined with low cuboidal epithelium. There were focal areas of the fœtal type of follicle. The stroma showed areas of calcareous degeneration and was infiltrated with the foreign body type of giant cell.

The patient made an excellent operative recovery in spite of a short period of auricular fibrillation observed the third day following operation. The basal metabolism dropped to plus 12 per cent. and the pulse to 80 on the ninth day after operation, and to plus 10 per cent. on the thirteenth.

Seen a year later, November 10, 1923, she seemed essentially well, although a hypertension of 200/70 was still present. There was no recurrence of the goitre.

Comment. — This represents fairly toxic adenomatous goitre, a disease which we are willing to agree with Plummer is probably distinct from exophthalmic goitre. The symptomatology and pathology both are markedly different in this case from those of Graves' disease.

It is of interest that this patient had had previously for years undoubted endemic colloid goitre, as she had been born and brought up in a goitrous district. Multiple adenomata gradually developed on this foundation, which is, as we have noted in the text, a frequent occurrence, and in middle life for some reason these take on increased function and produce hyperthyroidism.

Operative removal of the goitre relieved satisfactorily the symptoms with the exception of the hypertension, and this in all probability was not related to the goitre. The paroxysm of fibrillation after operation is fairly common in these cases. Had such been observed before operation, quinidine prophylactically might have been used.

Whether the iodine administration induced the hyperactivity of the adenomata, no one can say. It is possible, and some writers consider such an effect frequent, but against that we must set the fact that in many more cases the hyperactivity comes on in just the same way although no iodine has been given.

Case No. 4220. *Adenomatous Goitre Producing Pressure but not Hyperthyroidism.*

History and Examination. — A Polish metal worker of twenty-eight first seen on September 21, 1926 complained of productive cough and choking sensation for twelve weeks and showed a right sided goitre which had been present for six years. This was of moderate size and consisted of one large and several small nodules. The trachea apparently was pushed to the left, and the isthmus and left lobe of the thyroid were not enlarged. There were no symptoms or signs of thyroid over- or under-function. There were no eye signs. His general health had been good. Physical examination, save for the goitre, was not remarkable. The basal metabolic rate on September 25, 1926 was plus 3 per cent., pulse 74. X-ray of the chest showed a normal sized heart and no mediastinal tumor. The trachea, however, could be shown displaced to the left. The lung fields were clear.

Management. — A diagnosis of adenomatous goitre with normal function was made, but it was thought that there might also be a chronic broncho-pulmonary lesion as well, although the negative X-ray was against this.

On September 27, 1926 the right lobe of the thyroid was removed under novocaine. The portion removed appeared to be an encapsulated tumor about the size of an orange. On section it showed a smooth, purplish-red surface with areas of calcification. Microscopically it showed follicles filled with colloid and lined by low epithelium. The stroma contained exudate.

The patient made an uneventful recovery and promptly got over his cough. On October 9, 1926 his basal metabolism was minus 13 per cent., pulse 76; and on December 8, 1926 it was plus 5 per cent., pulse 68.

Seen for check up on June 21, 1927 he presented no symptoms, and

had a small amount of thyroid tissue palpable on the left. Basal metabolism was minus 3 per cent., pulse 64.

Comment. — This case illustrates well benign adenoma of the thyroid producing no thyrotoxicosis, but giving rise to definite displacement of the trachea and pressure symptoms. It is of more than passing interest that a productive cough sufficient to suggest actual broncho-pulmonary disease rapidly disappeared when the goitre was removed.

Histologic examination showed that the adenoma was of the adult type. A lesion of this sort easily might have given rise to hyperthyroidism later in life.

CASE NO. 3416. *Adenomatous Goitre with Slight Hyperfunction Relieved by Adenectomy with Later Development of Further Adenomata*

History and Examination. — A married Polish woman of thirty-eight, who had had two children, presented herself at the clinic on August 22, 1925 for treatment of a goitre which had been present for ten years or more. It had slowly grown larger and at times had given rise to a choking sensation and some difficulty in swallowing. For a few weeks only she had had some nervousness, and this was the only symptom suggesting hyperthyroidism that could be elicited.

The right lobe of the thyroid was found enlarged to the size of an orange; it was smooth, firm, non-tender and over it could be heard a faint bruit. The superficial veins in the neck in the region of the goitre were markedly engorged. There was a slight tremor of the extended fingers, but no eye signs or other physical signs of importance. The basal metabolism was elevated as shown below.

Management. — A diagnosis of adenomatous goitre was made. It was thought that a certain amount of cystic degeneration had taken place and that probably there was some hyperfunction.

Operation was performed on September 2, 1925 under gas and oxygen. A single encapsulated tumor, 6 cm. in diameter, was found in the right lobe. This was shelled out of the normal thyroid tissue which had been crowded anteriorly and downward. Afterwards another nodule 2 cm. in diameter was found and removed. On section the larger tumor proved to be made up of hæmorrhagic and cystic tissue without normal thyroid markings. Microscopically it showed typical adenomatous tissue of the fœtal type.

She made a good recovery from the operation. The metabolism dropped and she gained weight and for about a year remained well. Then some slight nervousness returned and a new adenoma appeared on

the left, which when last seen on July 19, 1927 was the size of a walnut. Other smaller masses were felt at that time in both the right and left lobes. The metabolism rose slightly but did not exceed normal limits. The various metabolism observations were as follows:

Date	Basal Metabolic Rate	Pulse	Wt. in Kg.	Remarks
Aug. 6, '25	+39	100	56.7	
" 12, '25	+46	101	56.8	
" 27, '25	+25	97	55.5	
Sep. 2, '25				Operation
" 11, '25	+9	74	52.4	
Oct. 8, '25	−11	62	56.7	
" 30, '25	−3	66	58.8	
Jan. 27, '26	+3	69	62.9	
Apr. 23, '26	+5	74	64.8	
Jun. 2, '26	+4	70	64.9	
Dec. 8, '26	+9	76	61.1	New adenomata growing.
Mar. 10, '27	+11	72	60.9	
Jul. 19, '27	+6	72	59.0	

Comment. — Another case of adenomatous goitre, this one of the fœtal type and with slight hyperfunction. Enucleation of the original adenomata with the balance of the thyroid left in situ caused a prompt restoration to an apparently normal status.

A year later new adenomata were clearly developing, and later on these may cause further hyperthyroidism. Regrowths of adenomatous tissue in this way are by no means uncommon. The possibility must be borne in mind in making operative prognoses.

Case No. 4114. *Adenomatous Goitre with Hyperthyroidism with Permanent Auricular Fibrillation*

History and Examination. — An Irish housewife of seventy, seen first on July 20, 1926, had had a goitre for seven years. It had slowly enlarged. For a year and a half she had had marked dyspnœa and palpitation on exertion and increasing nervousness and dry cough. There were no eye signs. The goitre was assymmetrical, largest on the left, pushing the trachea to the right and was without thrill or bruit. There was

slight tremor of the fingers. The heart was definitely enlarged transversely with systolic murmur at the apex and total arrhythmia. Elec-

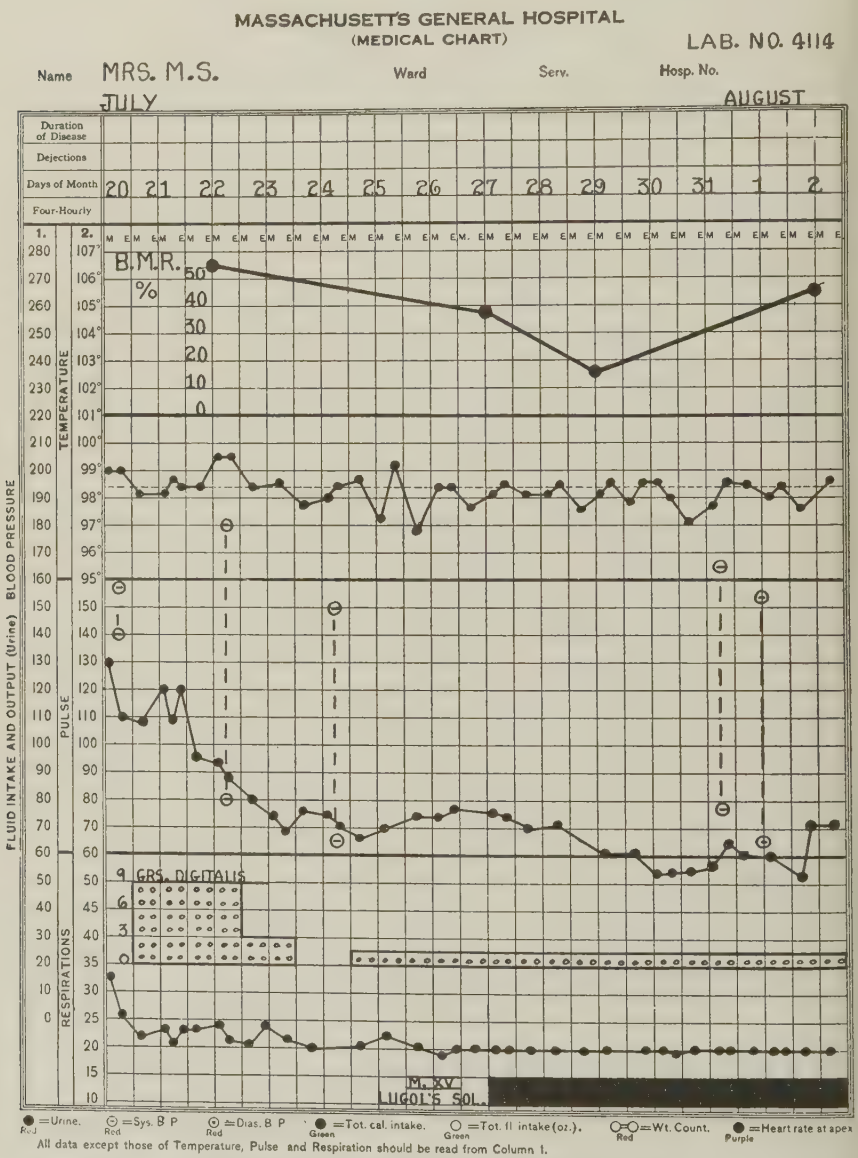

FIGURE 42. *Adenomatous Goitre with Hyperthyroidism and Permanent Auricular Fibrillation.* Clinical chart in Case No. 4114.

trocardiogram showed auricular fibrillation, and the pulse rate at the wrist was 146, the blood pressure 170/140.

Management. — A diagnosis of adenomatous goitre with hyperthyroidism and thyroid heart disease was made, and operation decided upon. The clinical chart with medication is shown in Fig. 42. Digitalis produced a marked slowing in pulse and increase in pulse pressure. Lugol's solution given subsequently caused but little further slowing.

On August 3, 1926 a single, large, encapsulated adenoma, 8 cm. in diameter, was shelled out of the left lobe of the thyroid under ethylene. Two small nodules were felt in the right lobe, but on account of the cardiac condition the operation was not extended to include resection of these. The tumor on section was dark red and at one point calcified. Microscopic examination showed essentially normal follicles with moderate amount of colloid and increased interstitial tissue.

The patient stood the operation well. Her case has been followed for sixteen months since, during all of which time her heart has continued to fibrillate. The metabolism has remained somewhat elevated varying between plus 14 per cent. and plus 39 per cent., perhaps owing to some residual hyperthyroidism from the adenomata remaining in the right lobe. Lugol's solution had no noteworthy effect on this residuum, either symptomatically or metabolically. The remaining slight cardiac symptoms responded somewhat to occasional courses of digitalis.

Case No. 4486. *Adenomatous Goitre with Hyperthyroidism. Prompt Relief by Hemithyroidectomy*

History and Examination. — A housewife of fifty-one, born and raised in Switzerland, entered the hospital February 1, 1927, complaining of a goitre which had been noted first a year before, of nervousness and increased irritability for three to four years, of cough and choking sensation for two years, and of dyspnœa, palpitation, œdema of the feet and increased sweating for eight months. There was found in the region of the right lobe and isthmus of the thyroid a peach-sized nodule, the lower pole of which dipped beneath the sternum. It was soft and without bruit, but the veins over it were engorged and the carotids beat violently. The trachea was noticeably displaced to the left. There were no eye signs, but the skin was hot and moist and there was a slight tremor. The heart was remarkable only in its hurried action. The blood pressure was 170/80. X-ray showed a tortuous aorta but no intrathoracic goitre.

Management. — A diagnosis of adenomatous goitre with hyperthyroidism was made, and operation decided upon. The course of events is

indicated in the chart. Lugol's solution was given but not with the expectation that it would have any noteworthy effect on symptoms or metabolism. It did not.

At operation, under novocaine, on February 18, 1927, the right lobe of the thyroid was resected. The left lobe felt normal and was allowed to remain. The tissue removed appeared to be an encapsulated tumor the size of a peach, which on histologic examination gave the picture of colloid goitre.

She made a satisfactory recovery and eight months later had no

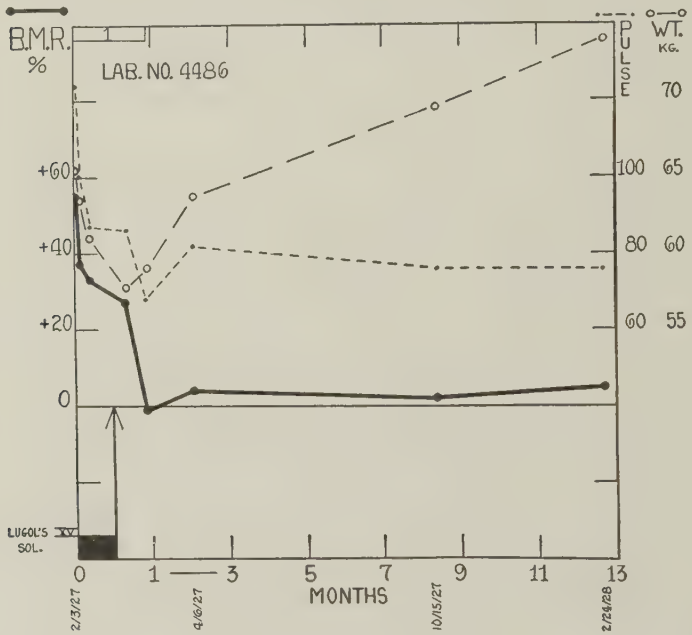

FIGURE 43. *Adenomatous Goitre with Hyperthyroidism* (*Case No. 4486*). Prompt relief following hemithyroidectomy.

evidence of goitre or hyperthyroidism remaining. She was, however, having metrorrhagia, hot flashes and slight pitting œdema of the ankles.

Comment. — This case is presented chiefly as an instance of as nearly classic adenomatous goitre with hyperfunction as can be found. The thyrotoxic symptoms were marked, yet the nervous phenomena were not as marked as in Graves' disease, whereas the cardiac, relatively at least, were somewhat more so. There was also slight but definite evidence of pressure, very common in this disease but rare in exophthalmic goitre;

the trachea is far more likely to be displaced by the assymetrical adenomatous than by the symmetrical hyperplastic goitre.

It is of interest that Lugol's solution had but little effect, in contrast to that in Graves' disease, and that hemithyroidectomy brought about a normal status with metabolism quite within normal limits, which it seldom does in Graves' disease.

Case No. 5316. *Partially Intrathoracic Goitre of Moderate Size, Illustrating Early Signs of Pressure*

History and Examination. — A Russian baker of fifty-two, entered the hospital November 22, 1927, complaining chiefly of headaches. Two years ago the patient had several attacks of diplopia coming on suddenly and lasting several days. Three months ago the family noticed that he moved slowly and was retarded in thought and action. He would not enter into conversation or answer questions. About the same time a puffiness of his neck on both sides above the clavicle was noted, spreading two months ago to the face. One month ago he began to have sudden headaches once or twice daily located at the top of his head. At the same time he began to have a productive cough; he was observed to snore more loudly at night, and dyspnœa on exertion increased.

Examination showed a short stocky man with a thick neck. Above both clavicles there were soft non-tender pads of flesh, somewhat greater on the right. The eyelids were puffy, and the face seemed somewhat congested. The hands were slightly cyanotic and their veins emptied less readily than usual. The skin was dry and scaly, but there were no signs suggestive of myxœdema. The thyroid did not feel enlarged. When he swallowed, a mass was palpable rising behind the right sternoclavicular joint. Enlarged collateral veins between the neck and thorax were not visible. The lungs showed evidence of chronic bronchitis and emphysema. Neurologic examination was negative aside from slight blurring of the mesial aspect of the left optic disc. On the ward his mental status appeared to be normal. On November 25th his basal metabolic rate was plus 12 per cent., his pulse 88, and his weight 70.9 kilos. X-ray showed "the heart shadow obscured by the position of the diaphragm but its transverse diameter is increased to the left in the region of the ventricle. There is no increase in the supracardiac dulness, but the aorta is tortuous and distinctly prominent in the region of the knob. Above the heart shadow is a triangular area of dulness somewhat wider than the supracardiac shadow and which disappears in the shadow of the neck. The trachea is displaced to the left. The changes in the lungs are those of chronic lym-

phatic enlargement with emphysema. The appearance of the heart is that of arteriosclerosis and slight hypertrophy of the left ventricle. The shadow in the upper mediastinum may be due to intrathoracic goitre". Urine examination was negative. Renal function by phenolphthalein was normal; the non-protein nitrogen of the blood was 40 mg. per 100 c.c.

Management. — The impression of change in mentality observed by the patient's family was not borne out by observation in the hospital. There was evidence, however, of pressure upon veins entering the superior thoracic aperture, œdema of the tissues of the neck and face, and a palpable mass deep behind the right sternoclavicular joint. These signs pointed to a mediastinal tumor, a diagnosis which was confirmed by X-ray examination. The probable cause of such a tumor was an intrathoracic goitre. In view of the negative neurologic examination operation was advised.

Since respiratory obstruction was possible, anæsthesia was by local infiltration with novocaine. A transverse incision was made, dividing the ribbon muscles on the right. The right lobe of the thyroid was felt to descend through the superior thoracic aperture. The superior pole and lateral veins were tied off, the thyroid tissue cut through, and the lobe delivered and removed, except for a small amount of tissue in the region of the parathyroids and recurrent nerve. It contained four encapsulated nodules, the largest 8 cm. in greatest diameter, showing microscopically the structure of colloid goitre. The left lobe was normal in size, consistency, and position, and was not disturbed. The patient made a good convalescence, and was discharged relieved on the ninth day.

Comment. — In this case attention was directed away from the lesion by nervous symptoms of obscure type. It illustrates the effects of pressure upon veins and trachea at a time when they might have been overlooked. However, the diagnosis of a mediastinal mass was readily made, by careful palpation in this instance, and its limits determined by X-ray examination. In view of the essentially negative physical and neurologic examination, removal of this intrathoracic goitre of moderate size was indicated, although its presence could not explain the whole symptomatology.

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CHAPTER VIII

MYXŒDEMA AND CRETINISM

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So much has been written about these classic syndromes that it would be idle here to enter into any but the barest outline of their essential characteristics. Both the history of their recognition and the usual symptoms related to the outstanding physiologic variation, hypometabolism and water retention, have been traced in a previous chapter. Our remarks will be directed for the most part toward certain points in diagnosis and treatment that have come up in our own experience, and certain studies that have been made on the morbid physiology by some of our associates. As myxœdema is the simpler condition it will be discussed first.

Myxœdema

Diagnosis

Diagnosis, as in the case of exophthalmic goitre, generally offers no difficulties. It is based on the cardinal symptoms and signs of the disease; puffiness of the face, thickening and dryness of the skin, brittleness of the hair, chilliness, mental sluggishness, etc., and the demonstration of a lowered basal metabolism.

Differential diagnosis is chiefly from chronic Bright's disease, non-myxœdematous hypometabolic cases, once in a while from various sorts of anæmia including pernicious and rarely from organic heart disease. Hypertension may exist with, but is not a part of, myxœdema. The puffiness of the face is what suggests Bright's disease, and when this is coupled with hypertension and perhaps a little albumin in the urine, the mistake is not absolutely, though perhaps nearly, unpardonable. The heart in myxœdema is often dilated, and it beats feebly. The changes in the electrocardiogram resemble those seen in myocardial damage. Consequently, myxœdema may be mistaken for primary cardiac disease. In similar fashion, the marked anæmia, which often accompanies myxœdema, may be taken for a primary affair. We have seen both myxœdema mistaken for pernicious anæmia, and pernicious anæmia mistaken and treated for myxœdema. They may coexist. The non-myxœdematous low metabolic rate cases are not mistaken for definite myxœdema; they are presumably called atypical myxœdema by some, solely because of the low rate. Finally, myxœdema is to be differentiated from pituitary cachexia, which it resembles, because in each there is a low metabolic rate.

The separation of nephritis, heart disease and various sorts of anæmia is based, of course, on adequate clinical and laboratory

studies; the finding on the one hand of positive evidence of these other conditions or on the other of the pathognomonic evidence of myxœdema.

It should be emphasized thoroughly that failure to recognize myxœdema is little short of a calamity, for it is one of the few diseases for which we possess a specific cure. Yet this is repeatedly being done. If Dr. A treats Mrs. X for two years for Bright's disease with no improvement, and then Dr. B, recognizing her condition as myxœdema, cures her in two weeks with pills, the community is going to give Dr. A very little credit.

Symptomatology

Sturgis[1] recently has made a careful analysis of fifteen cases, and Krantz[2] has been over and analyzed the symptoms in forty-five consecutive cases at the Massachusetts General Hospital. The latter's findings are given in the table on page 289.

Etiology

Of the cause of spontaneous adult myxœdema, other than that it is due to atrophy of the parenchyma of the thyroid, nothing definite is known. Some writers fancy that it represents the end result of an inflammatory process in the gland, or thyroiditis. This perhaps may be true in certain cases, but that it is the sole cause is very unlikely; a history suggesting a previous thyroiditis is obtained only very rarely. There is a certain ill-defined relation to endemic goitre. Goitrous persons may become myxœdematous, probably more frequently than non-goitrous, but since the disease does occur quite typically in absolutely non-goitrous persons and in non-goitrous regions, one is left in a quandary as to the relation between the two.

The greater frequency in women is variously given as from

Symptoms	Percentage of patients in whom symptoms were present.	Symptoms	Percentage of patients in whom symptoms were present.
Œdema:		Neurological:	
Eyelids	95.4	Numbness and Tingling	82.5
Face	95.2	Slow Speech	87.5
Hands	72.5	Thick Tongue	85.0
Ankles — non-pitting	80.0	Sense Organ Impairment:	
Ankles — pitting	43.9	Eyesight	43.2
Facies — Myxœdematous	85.4	Hearing	40.5
Fat Increase:		Skin:	
General	88.1	Paleness	100.0
Abdominal Wall	73.7	Cyanosis	33.3
Thighs	20.6	Dryness	100.0
Supraclavicular	51.3	Scaling	77.7
Weight Increase	94.9	Hair:	
Gastro-Intestinal:		Loss from Head	82.9
Constipation	92.7	Coarseness	71 8
Indigestion	75.0	Loss from outer $\frac{1}{3}$ of Eyebrows	63.9
Nausea	39.5	Loss in Axilla	73.0
Vomiting	39.5	Loss of Pubic Hair	51.3
Joints:		Nails — Brittleness	70.0
Elbows	18.9	General Symptoms:	
Knees	56.4	Appetite	43.8
Other	34.2	Sensation of Cold	97.6
Mental:		Frequent Upper Respiratory Symptoms	32.4
Drowsiness	92.5	Dizziness	66.7
Memory Impairment for Past Events	12.8	Dyspnœa	90.0
Memory Impairment for Present Events	81.6	Fatigue	100.0
Emotional States	73.7	Headaches	70.0
Psychoses	21.6	Absence of Sweating	97.4
		Weakness	100.0

6 to 1 to 10 to 1. In the latest Massachusetts General Hospital series there were 13 males to 64 females. In women the onset of the disease is very prone to coincide with or follow some event in sexual life. In Krantz's series, for example, it began in 10 at the menopause, in 12 after childbirth, in 4 after operation on the pelvic viscera, in 2 after acute infections and in 13 no obvious cause was recognized. The age at the time of onset

in the four males averaged 48, that in the females is indicated in Fig. 44. The relation to sex events in the female may mean nothing more than that at these times metabolism is accelerated and the strain upon the thyroid consequently greater. On the other hand, it may signify the breakdown of some delicate inter-endocrine balance in which the thyroid is but one of several members. Since the complete picture can be produced through surgical removal of the thyroid, the former and simpler explanation in the case of the spontaneous disease is preferable.

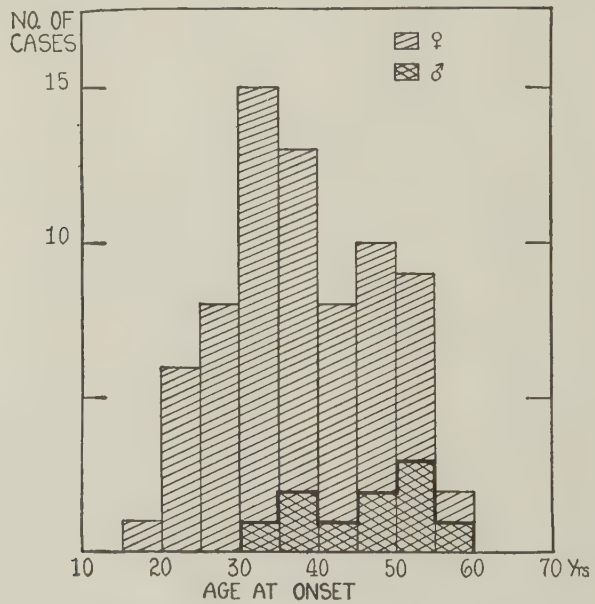

FIGURE 44. *Adult Myxœdema.* Age distribution curve in 82 Massachusetts General Hospital cases.

Pathology

Nowadays autopsies on patients with myxœdema are very rare. In the whole series of 8300 autopsies at the Massachusetts General Hospital there have been but seven. The reason for this is obvious; persons no longer die of this disease, and only by a rare coincidence will autopsies be obtained on myxœ-

dematous patients dying in hospitals of another disease. In one of the Massachusetts General Hospital cases (No. 3797) death was due to cardiosclerosis with heart block and in another to extensive chronic bronchiectasis. Autopsies on untreated cases will be rarer still (only three in our own series), but fortunately a series of twenty was collected in the myxœdema report of the London Clinical Society in 1888[4], before the treatment had been discovered. In this series the only constant change was in the thyroid and was in each instance of the same nature. The chief findings of the investigating committee were: "The morbid condition seems to begin as a small-celled infiltration of the walls of the vesicles, and this is accompanied or soon followed by epithelial proliferation in the vesicles themselves.

"In a more advanced stage the gland becomes converted into a delicate fibrous tissue in which clumps of small round-cells, clearly the remains of the vesicles, are scattered. In the last stage the gland structure is replaced by fibrous tissue, in which small islets of round-cells are sparsely placed.

"It may be observed here that in most of the fatal cases the thyroid gland exhibited very advanced and general structural alteration, but that in a few the pathological change was comparatively in an early stage. In one indeed (Mr. Barling's), the glandular elements in some places showed very little departure from the normal state; but in other sections the characteristic morbid change was very obvious. It would appear therefore that death may ensue before the affection of the thyroid gland becomes advanced, and also before the entire gland becomes invaded.

" . . . As regards the skin, we have found very frequently the nuclear hyperplasia and the development of connective tissue which Dr. Ord describes in his original paper, and these

changes occur mainly in the neighbourhood of the sudoriparous and sebaceous glands, and around the hair-follicles. In a few instances the Sub-Committee has noticed an unusual interval between the bundles of fibrous tissue in the corium. This open-textured condition is, however, quite exceptional, and it differs in no respect from what is seen in ordinary œdema."

. . . . . .

"The increase in bulk so frequent in myxœdema is due to an overgrowth of the subcutaneous fat, as is clearly shown by the results of post-mortem examination. The loss of hair, the absence or diminution of perspiration, and of the secretion of the sebaceous glands, may reasonably be ascribed to the anatomical lesions which are so often seen in the skin.

"Interstitial changes in the internal organs have not infrequently been found, as will appear from the detailed account already given. These changes are most common in the kidney, and they presented the ordinary features of interstitial nephritis, though very often of no great intensity. The Sub-Committee, however, is of opinion that such alterations, so frequently found as they are in persons of adult or advanced life dying from various causes, cannot be considered peculiar to myxœdema.

"The liver was healthy in rather more than half the cases, and when alterations were present they were usually either partial or slight. Indeed, in two or three instances there is still some doubt whether the appearances were not within the limits of the normal state.

"In two cases out of the nine examined the heart presented changes of the same nature, one exhibiting an early stage, and one a comparatively advanced stage of interstitial myocarditis. It may here be observed that in neither of them was there any history of syphilis. In the remaining two thirds of the cases the organ was healthy.

"The changes in the sympathetic, though frequent, are not constant, and for this reason, and also on the ground that the superior cervical ganglion was usually the only part examined, the Sub-Committee feel that they are not justified in ascribing to such changes any importance from an etiological point of view.

"The thickening of the adventitia of the arterioles, originally described by Dr. Ord, has been very often seen by us, but in only one instance was there evidence of any overgrowth of the perineurium of the cutaneous nerves."

In the three of our autopsies, which were on untreated patients, the myocardium was dilated, pale and flabby, and there was marked interstitial edema.

Functional Pathology

Of the functional pathology more is known. In an earlier chapter (Chap. I) the historical development of our knowledge of hypometabolism resulting from athyreosis has been outlined. The symptoms resulting from lowered heat production per se have been identified. Besides lowered heat production, which is invariably present[5, 6, 7], the following functional alterations, among others, likewise may be said to be characteristic of the hypothyroid state and probably dependent upon the primary metabolic fault:

1. Decreased rate of volume flow of blood, a natural sequel to decreased oxidation, although, as Bock[8, 9] and his coworkers have found, the reduction in blood flow may be even greater relatively than that in metabolism; decreased systolic discharge from the heart, decreased pulse pressure and flabby state of heart muscle as shown by certain characteristic changes in the electrocardiogram[10].

2. Diminished rate of exchange of calcium and phosphorus; as Aub[11] and his coworkers have shown, these substances are deposited in greater concentration in the bones and eliminated less freely in the urine and stools than they are in the normal individual; their actual concentration in the blood is not altered greatly.

3. Altered distribution of body fluids, crystalloids and colloids with decreased total plasma volume, decreased concentration of plasma, water and chlorides and increased protein, as Thompson[12] has found. Coincident with these changes there is an increased storage of water in the tissues. The spinal fluid protein, so Thompson and collaborators[13] have also shown, is increased. The ratio of spinal fluid chloride to plasma chloride is increased, owing apparently to the increase in concentration of plasma protein.

4. Increased storage of deposit protein, as Boothby and collaborators[14] have calculated from the total weights and nitrogen loss of myxœdema patients after the injection of thyroxin, assuming that since their diet covered their caloric needs, total weight loss represented largely water loss.

5. Reduced irritability and reactivity of (*a*) the central nervous system, as shown for example by diminished perception of sound, impaired memory, and diminished reflexes, and (*b*) of the vegetative nervous system, as manifested perhaps in diminished secretory and peristaltic action.

6. Retardation in rate of growth of all tissues, as shown in the adult for example by decreased hæmatopoiesis with resulting anæmia[15, 16], and by the slower growth of hair and nails.

7. Hypercholesterolemia, usually varying inversely with the metabolic rate. This is of value in differential diagnosis between true myxœdema and other forms of hypometabolism.

8. Reduction in blood iodine concentration. This involves

chiefly the alcohol-insoluble fraction which may practically disappear.

9. Diminished tolerance to morphine and digitalis.

Of course there are many other departures from normal function in hypothyroidism, such, for example, as a prolongation of the blood sugar curve and perhaps a raised renal threshold for sugar[17], but as yet these are not as clear cut as the ones enumerated above.

When thyroid or thyroxin is given to the myxœdematous subject, heat production rises toward normal and with this rise the symptoms and physical signs of the disease depart. Structural lesions, save those in the thyroid itself, disappear, and the following restorations to normal function ensue:

1. The heart resumes a normal tone, rate of beat, output per systole and total output per minute. Pulse pressure increases, and the electrocardiogram assumes a normal shape.

2. Coincident with increased energy exchange, the exchange of calcium and phosphorus increases to a normal rate[11].

3. Water migrates from tissues to blood stream and out through the kidneys. In this manner, as the diuresis occurs, the œdema disappears. In the process a certain increased quantity of fluid remains in the vessels with resulting rise in plasma volume[12]. The concentration of chloride in the plasma rises, that of protein falls[12]. The ratio of spinal fluid chloride to plasma chloride decreases[13].

4. A marked but temporary rise in nitrogen outgo occurs, which Boothby and his collaborators[14] think is due to the destruction of the extra deposit protein laid down during the preceding hypothyroid state.

5. The nervous system, central and vegetative, takes on a normal function, which may be observed in improved memory,

more acute sensation (e.g. hearing), improved reflexes and increased peristaltic and secretory activity (e.g. free bowel action and sweating).

6. There is an increase in the rate of growth, (*a*) of the organism as a whole, as seen in juvenile myxœdema, (*b*) of the skin, hair, and blood, as seen in the adult. Men with myxœdema may need to shave only every three or four days; after they receive thyroid their hair growth is accelerated so that daily shaving is necessary.

7. Blood cholesterol returns to normal.

8. Blood iodine returns to normal.

9. Tolerance to morphine and digitalis is restored.

The effect of the hormone, as would be the case with any catalyst, is greatest when its concentration at the start is lowest. For instance, Thompson and collaborators[18] in the Massachusetts General Hospital thyroid clinic have found in a certain case of myxœdema that 10 mgm. of thyroxin given intravenously, when the basal metabolism is minus 40 per cent., causes an elevation of 38 points to minus 2 per cent., the peak being reached on about the fifth day and the effect lasting over a period of about eighty days. In this same case, when as a result of giving thyroid by mouth in the dosage of three grains daily the basal metabolism had assumed a constant level of minus 4 per cent., if 10 mgm. of thyroxin were given intravenously the metabolism rose only 20 points to plus 16 per cent.; the peak was reached on about the fourth day, and the effect lasted but twenty-two days. A similar result has been obtained with thyroxin at different metabolic levels in another case, and in many cases the administration of a given quantity of thyroid by mouth has been found less effective at a normal than at a low level of metabolism[12].

Treatment

The treatment of myxœdema can be summed up in the one word, thyroid. The isolation of thyroxin by Kendall is a physiologic discovery of first magnitude and has contributed vastly to our knowledge of the morbid physiology of myxœdema in particular and to the physiology of the thyroid in general; to the treatment of hypothyroid states, however, it has in our opinion added nothing.

According to a recent textbook writer, "Thyroxin is far superior to dessicated thyroid because its strength is known; it is many times more powerful; and the quantitative relationship between the amount of thyroxin administered and the basal metabolic rate permits the daily dosage to be accurately measured"[19].

With these statements we disagree. Thyroxin is not superior to dried thyroid gland in the routine treatment of the disease because its strength is known, nor for any other reason that we can perceive. It is superior in clinical research because of its known strength, and for that purpose we have used it often, but to recommend it to the practitioner as superior to dried thyroid, we believe entirely unwarranted. In the first place, to exert its full effect it must be given parenterally, for by mouth its action is very uncertain; sometimes it is even completely inert. Given subcutaneously or intramuscularly it is apt to cause painful local reactions just as pituitrin does. To possess the virtue claimed by the writer quoted above, it must be introduced by the intravenous route. In general, any intravenous therapy is to be avoided, when the desired effect can be secured by introduction of the agent through a more usual route. The profession is by far too free nowadays with intravenous medica-

tion. Moreover thyroxin administered intravenously even in doses of no more than 10 mgm., the dose usually recommended, can give rise to exceedingly unpleasant and possibly dangerous reactions. These we have observed to take the form of fever, severe cramp-like pain, tenderness of all muscles in the body, nausea and not infrequently, vomiting. There may be marked tachycardia. The cramps and nausea may last three or four days, and the muscle soreness for three or four weeks. At times, even after no more than 10 mgm. of thyroxin, the reaction may be distinctly alarming.

The writer quoted above also says, "Patients should be warned to expect this reaction and should be advised that it is essential to their improvement". Since patients with myxœdema can be rendered symptom-free readily with no reaction whatever by taking whole thyroid gland by mouth, as they have been since the days of Murray, to say that the distressing reaction is essential to their improvement appears to us quite unjustified.

Furthermore, the intimation that thyroxin is more desirable because stronger is rather pointless, since adequate dosage of dried gland is often no more than a few grains per day. Finally, it is quite as easy to check the dosage of whole thyroid by basal metabolism determination as that of thyroxin, although perhaps less necessary.

During the early years of treatment of thyroid disease with basal metabolism control in the Massachusetts General Hospital clinic (1913–1919), it was believed that a thyroid ration sufficient to maintain the patient's basal metabolism within the range of standard basal metabolism should be determined carefully for each patient with myxœdema. While this usually is all right, our views have been modified somewhat by wider experience.

In the first place, it should be emphasized that there is no fixed level of metabolism optimum for all so-called normal persons. Neither is there any proof that any given patient is better off with a metabolic rate of minus 8 per cent. than with one of plus 6 per cent. Many apparently healthy persons habitually have rates well below the arbitrary minus 10 per cent. of normal standards, and patients with myxœdema are frequently symptom-free with rates of minus 18 per cent. or minus 20 per cent. We are swinging round, therefore, to the view that a symptom-free state is the correct guide in gauging thyroid dosage in myxœdema, rather than maintenance of any selected level of metabolism. Furthermore, since overdosage may do serious harm, in general we believe that the lowest rate at which no symptoms of myxœdema remain should content us.

It is a fact of considerable interest, and one not generally appreciated, that myxœdematous patients are more susceptible to enteral thyrotoxicosis than normal persons. The right dose of thyroid renders the myxœdematous patient symptom-free; an excessive dose readily makes him thyrotoxic.

Christian[20] has made a good point, and our experience coincides with his, that to boost suddenly the basal metabolic rate, and consequently the blood flow and heart work, of a patient whose circulation has been accustomed to functioning for years at a level perhaps 40 per cent. below normal is a procedure of very questionable wisdom. We agree most heartily with this attitude. There is certainly no hurry in a disease as chronic as myxœdema, except in the very terminal stage of the cachexia, and to run the risk of a severe immediate reaction and perhaps later the production of untoward cardiac symptoms by the intravenous administration of thyroxin cannot be discouraged too much. Even with thyroid itself harm may be done

by too rapid initial dosing. It is far better for a practitioner to feel his way slowly with conservative dosage, and to take his time in the discovery of the optimum daily maintenance ration. When the patient is handled in a cautious manner, basal metabolism determinations need not be made at frequent intervals. In fact a good clinical observer could dispense with them entirely, both in diagnosis and treatment, governing his management entirely by symptomatology. We do not wish to be interpreted as discouraging metabolism tests; they are always helpful, and in our own clinic we make use of them very frequently in the conduct of myxœdema. It is a mistake, however, to suggest that they are absolutely essential for good work.

It is usually proper in fully developed myxœdema to start with 0.2 gm. (three grains) of thyroid a day. In the course of a week a change will be noted, and in a month symptoms may be largely gone. When they are, it is well to reduce the dose perhaps by half, and see whether they recur. If they do, a slight increase may be made, and then in the weeks that follow shifts may be made from time to time, preferably not oftener than once a fortnight, until the optimum maintenance ration has been discovered.

In our cases the maintenance dose in most instances has varied from 1 to 3 gr., the majority requiring $1\frac{1}{2}$ gr. The brand of thyroid used will make some difference. The physiologic action of thyroid, as pointed out by Marine and by Salter, Lerman and Means[37], is directly proportional to the total organic iodine content. The U. S. Pharmacopœia requires not less than 0.17 per cent. nor more than 0.23 per cent. by weight of iodine, and there must be no inorganic iodine or iodine in any other form of combination than that peculiar to the thyroid.

We have used the various preparations on the market and obtain fairly constant results with any brand. Those concerns which adhere to the Pharmacopœia, as for example, Armour Company, supply a product containing 0.2 per cent. iodine. Burroughs, Wellcome and Company label their material in terms of fresh gland which contains 0.08 per cent. iodine. Parke, Davis and Company put out a product containing 0.3 per cent. iodine. Lerman and Salter[36] found the following dosages equivalent: 0.35 mg. crystalline thyroxin, 1½ gr. U. S. P. thyroid, 1 gr. Parke, Davis thyroid and 5 gr. Burroughs, Wellcome thyroid. The important thing for the practitioner is to use a brand of constant strength, preferably one adhering to the U. S. P. standard, and with the effects of which he is familiar.

When administering thyroid, one should observe carefully the circulation and be on the lookout for circulatory symptoms. Of the latter, palpitation and precordial distress and pain are by far the most important. No patient should be given thyroid for any purpose without being cautioned to report at once, if palpitation or the slightest precordial discomfort should arise[22]. The myxœdematous patient may be rendered thyrotoxic by excessive dosage and exhibit the same symptoms that occur in normal persons on thyroid feeding.

It is, therefore, the duty of the physician, who inaugurates thyroid therapy in myxœdema or other conditions, to inquire about these various symptoms at intervals of not more than a few days, and to keep careful record of the pulse rate. In true myxœdema after the symptoms have been abolished and the maintenance dose established, the patient safely can be allowed to go on for long periods without further visits, but it is desirable to check up every six months, even when all is going well.

The treatment in all cases of spontaneous myxœdema of course will have to be continued for the rest of the patient's life.

The results of treatment are obvious. All the cardinal signs and symptoms disappear; the puffiness of the skin, the chilliness, the lethargy, the thick speech and the slow thought. Bodily strength and cerebral activity return to normal; the skin desquamates; the volume of urine greatly increases; the bowels move more regularly; the hearing improves, and every system of the body takes on accelerated activity. Unless there are accidents at the start, there is nothing to prevent the adequately treated myxœdema patient from living out his normal life expectancy. Without treatment the duration of the disease is about ten years or less, death occurring from extreme cachexia or intercurrent disease. With treatment perfect health may be enjoyed indefinitely. Murray's case first treated in 1891 recently died (1919) at the age of seventy-four[23].

Complications of Myxœdema and Treatment

A patient with myxœdema may have any of the acute diseases to which the normal individual is subject. If he is not treated with thyroid, his ability to stand them is undoubtedly reduced; when on adequate thyroid therapy, he probably is as resistant as a person of similar age with normal glands.

There are, however, two systems which may show characteristic deterioration, the cardiovascular and the hæmatopoietic. There seems to be a general belief that myxœdema predisposes to arteriosclerosis. This hardly has been actually proved, but at least it is true that spontaneous myxœdema usually develops at an age period when sclerosis is common. The coronary arteries may suffer with the rest, and it is a matter of fact that angina pectoris sometimes can be produced in myxœdematous

subjects by too rapid thyroidization. We have seen several such cases, and in one in particular, a maintenance dose only large enough to keep the basal metabolism at minus 15 per cent. had to be employed. It was maintained at a higher level, he suffered from angina on effort. Another such case is No. 1052 at the end of this section. It is not difficult to understand how this may come about[24]. It is well known that in most instances the symptom angina pectoris is produced by effort or strong emotion, both of which involve accelerated blood flow. A person, whose metabolic plane has been elevated suddenly, readily might embarrass his coronary circulation in an effort which would have been harmless on a lower metabolic plane.

An analogous phenomenon is presented by a case of P. D. White's[25]. A married woman of forty-one had had symptoms of thyrotoxicosis for nine months, goitre for four and frequent attacks of substernal pain radiating down the left arm to the tips of the fingers with numbing and followed by precordial and substernal ache which had become almost constant. The pain was increasing and was coming as often as every half hour, varying in severity, and relieved at once by nitroglycerine. She had slight exophthalmos and thyroid fullness with bruit, so there seems no doubt that it was straightforward exophthalmic goitre. The point of interest to us at the moment is that after subtotal thyroidectomy these anginal attacks stopped entirely along with the more usual thyrotoxic manifestations, just as they did in the myxœdema patient when the dose of thyroid was reduced. The explanation is probably similar. Both patients had adequate coronary capacity for a certain level of metabolism but not for a greater one, which disease in one instance, and medicine in the other, imposed.

It is interesting to note that a group of recent French

writers[26] reports two cases of myxœdema in which angina was produced by thyroid feeding, while paradoxically another group[27] reports a patient having both myxœdema and angina, in whom the angina disappeared under thyroid administration along with the symptoms of myxœdema.

The danger of producing anginal failure by thyroid therapy is by no means the only cardiac problem in myxœdema. Various writers[28,29,30] have described a special form of lesion, the myxœdema heart, consisting chiefly of a general flabbiness with dilatation of all chambers. The reason for regarding this as due to the myxœdema is that it is little affected by digitalis but promptly disappears under thyroid therapy. Studies of the heart in 48 cases of myxœdema have been reported from our clinic. The heart frequently is dilated and shrinks after thyroid medication. There is no true cardiac insufficiency except when independent heart disease is present as a complication. Cardiac dilatation and low tonus are part of the picture of myxœdema.

Of rather different order and significance are the cardiographic changes characteristic of myxœdema. These consist in a flattening or inversion of the T wave, together with a general decrease in potential in all deflections in all leads. This same low potential in all leads is found in the myocardial exhaustion of serious coronary sclerosis, and White, therefore, thinks it denotes a sluggish action of the heart in myxœdema. Under treatment with thyroid these changes disappear rapidly and the electrocardiogram becomes quite normal. White has interpreted this to mean that the administration of the hormone has restored to normal the action of the previously sluggish heart. The point that we should retain is chiefly that, whereas these cardiographic evidences of sluggish action occur in all

cases of myxœdema, genuine cardiac hypertrophy occurs infrequently.

The anæmia of myxœdema, perhaps hardly a complication, rather a symptom of the disease, probably is due to slow blood formation. In our clinic 60 per cent. of the patients had red counts under 4 million, and half of them had hemoglobin values under 70 per cent. The picture usually is that of mild hypochromic anemia, but occasionally it is of the classic pernicious type.

The anemia may improve under thyroid therapy, but sometimes the response is slow and inadequate. In such cases iron or iron and liver extract in full doses will raise promptly the blood to normal. The pernicious anemia coincident with myxœdema responds to liver quite as well as the idiopathic variety of this disease.

Illustrative Cases

Case No. 2289. *Spontaneous Adult Myxœdema Coming on During Pregnancy in a Woman Whose Husband had Exophthalmic Goitre*

History. — A married woman of twenty-four, mother of three healthy children, native of Massachusetts, entered the hospital December 10, 1923. Her chief complaint was a backache both in lumbar and dorsal regions, which had started during her last pregnancy but which, instead of going away when the baby was born five months before, had continued and grown worse. The pain was described as sharp, but steady rather than stabbing. She had not regained her strength since parturition, and for three months had had severe headaches chiefly in the right frontal and occipital regions. At times she had been dizzy. She also had noted an increasing drowsiness and chilliness, and for several months her face had appeared bloated. A thickness had appeared at the back of her neck like "a pad of fat". Her voice, she said, had gradually become husky and deeper pitched, and her thought and speech slow. At times she could hardly pronounce words, and her memory had become very bad. She

had occasionally felt numb all over, and had had attacks of painless cramps in the flexor muscles of her hands. She had gained thirty pounds in four months, the extra flesh seeming to be chiefly about the hips. For several weeks her hair had been falling out. She had sweat very little, but had noted no other change in her skin. Her appetite had become poor, but her bowels remained regular. She claimed to have been more nervous than usual since the other symptoms began. The past story contained no facts which were recognized as bearing upon the present trouble. It was of interest, however, that the husband had been suffering from exophthalmic goitre for a period of four years. His symptoms antedated hers, therefore, but had increased in intensity since hers began. The husband admitted that his wife's lethargy served, he thought, to increase his own irritability. It is of further interest that the husband's mother was also ill with exophthalmic goitre, and one of his sisters had had it several years before. This remarkable coincidence of opposite syndromes in husband and wife is depicted in Fig. 45.

Examination. — Examination showed an obese young woman with puffy eyelids, thick lips and tongue, round expressionless face, slow speech, and lethargy. There was no pitting œdema anywhere, but over the cervical spine was a large mass of fatty tissue. Subcutaneous tissue was also increased about the waist line. The skin was dry and harsh, but there was a little moisture in the palms. The pubic hair was scant and the axillary gone. The heart was not enlarged to percussion; there were no murmurs. Blood pressure was 130/85. The urine and blood were not remarkable, the latter showing 4,800,000 red cells and 90 per cent. hæmoglobin. The electrocardiogram showed a flat T_2 wave.

Management. — A diagnosis of spontaneous myxœdema was made, and thyroid therapy has been carried out over a period of four years at the present time. The dosage and the ups and downs of metabolism in relation to thyroid administration are well shown in the chart. In the beginning a large dose was given for a short time (December, 1923) with a characteristic rise in metabolism and improvement in symptoms. This dose was clearly too large for maintenance since it carried the metabolism up to plus 15 per cent., although no toxic symptoms were noted at the time. A reduction to 0.1 gm. (one and one-half grains) as maintenance dose, however, was followed in another month by a drop to minus 21 per cent. and a return of the hypothyroid manifestations. These disappeared a second time when the dose was increased to 0.3 gm. (four and a half grains) per day. On that dosage she returned to an essentially normal metabolic plane and remained free from symptoms for six months, during which time she became pregnant.

FIGURE 45. *Husband and Wife with Exophthalmic Goitre and Myxœdema Respectively (Cases No. 2294 and 2289).*

Facing page 306.

Half way through her pregnancy, entirely on her own initiative, she stopped taking thyroid. This, at a time when metabolic requirements are increased and in view of the possible effect it might have upon both herself and the fœtus, was most undesirable, though as a matter of fact no harm seemed to come of it. Just after delivery, again on her own initiative, she took 0.2 gm. (three grains) a day for a fortnight. The metabolism following this was plus 17 per cent., but there were no thyrotoxic symptoms. Thyroid was then omitted.

In the course of the next four months off thyroid she again developed the complete picture of myxœdema in quite as marked degree as at first. Thyroid was again given in increasing doses up to 1 gm. (fifteen grains) a

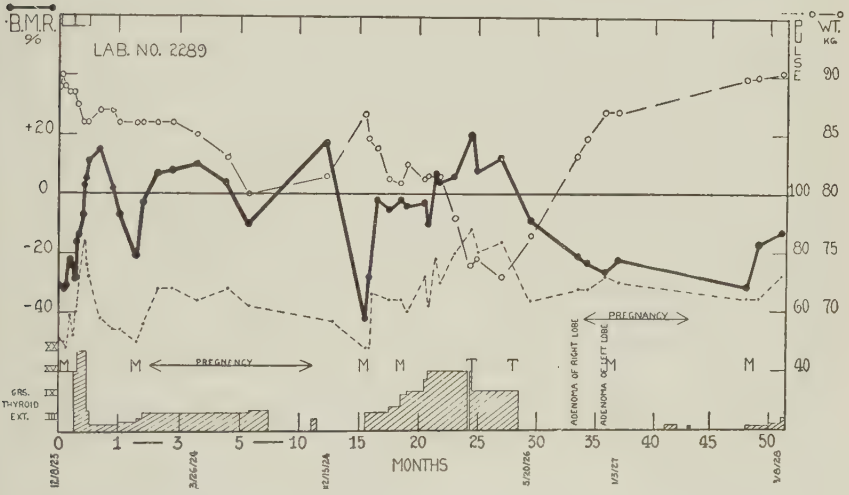

FIGURE 46. *Spontaneous Adult Myxœdema (Case No. 2289).* "M" signifies that clinical symptoms of myxœdema were present, "T" those of thyrotoxicosis.

day. After three months of this thyrotoxic symptoms occurred for the first time; palpitation, nervousness, tachycardia, and sweating, but these promptly stopped on a week's omission of the drug. They recurred, however, after four months on 0.6 gm. (ten grains) a day, so thyroid was again omitted.

For the next seven months (April to October, 1926) she felt well, although without thyroid. The metabolism slowly fell, but by no means as rapidly as it had done in the early part of 1925. A small adenomatous nodule was found in the region of the right lobe of the thyroid, and it was thought that in this might lie the explanation of the difference, for it

might well be contributing some thyroxin. Two months later a similar nodule was discovered in the left lobe. Some slight hypothyroid manifestations finally appeared, but the rate did not fall below minus 26 per cent., in marked contrast to the minus 42 per cent. and complete myxœdema of the previous omission. Furthermore, following this she went through another pregnancy. She was unwilling to come to the clinic during this period and took no thyroid until the eighth month. The child nevertheless was quite normal.

Comment. — This case represents typical spontaneous myxœdema in a woman somewhat younger than the average age for the onset of that disease. It apparently began during pregnancy, but the child did not suffer in consequence. As is usual, the cause of the athyreosis is entirely obscure.

The response to thyroid administration is well illustrated, together with the effects of both over and under dosage. The method of administration followed is obviously not ideal. For example, she should not have been allowed to get myxœdematous in March, 1925, or thyrotoxic in November, 1925. A dosage of 0.3 gm. (five grains) a day throughout would probably have kept her in a normal status. The omission during pregnancy was directly against indications, but as we stated above, the patient did this without orders.

The presence of clinical hypo- or hyperthyroid manifestations is indicated in the chart. For the most part they follow fairly closely the metabolic rate.

Her back and joint pain is of considerable interest. In the main these symptoms tended to be present when the metabolism was low and to disappear when the metabolic plane was forced up by thyroid. On the occasion of her first medicinal hyperthyroidism, when thyroid was omitted, the joint pain returned as the thyrotoxic symptoms disappeared.

Pains in the extremities and joints frequently occur in myxœdema and disappear, as here, with thyroid therapy.

Case No. 1052. *Spontaneous Adult Myxœdema in a Man with Anginal Pain from Thyroid Administration*

History. — A married lumber dealer of fifty-six, native of Massachusetts, was first seen in the clinic on June 14, 1921. A mixed tumor of the parotid had been removed two years previously. Since that time he had been getting stout (gain of thirty pounds) and sluggish. For two winters he had minded the cold far more than ever before, and enjoyed hot weather to an unusual degree. In cold weather he would sit by the stove

as much as possible and feel chilly even then. He had noted that his skin had become dry and scaly and his hands clumsy. His memory had become poor.

Examination. — Examination showed a sluggish, overweight, puffy, pasty faced, good natured individual with expressionless and stupid appearance and thick speech. The tongue was definitely thickened, the hair coarse and sparse, and the skin dry and scaly. He was slightly deaf. The heart was not enlarged. The pulse was 66 and the blood

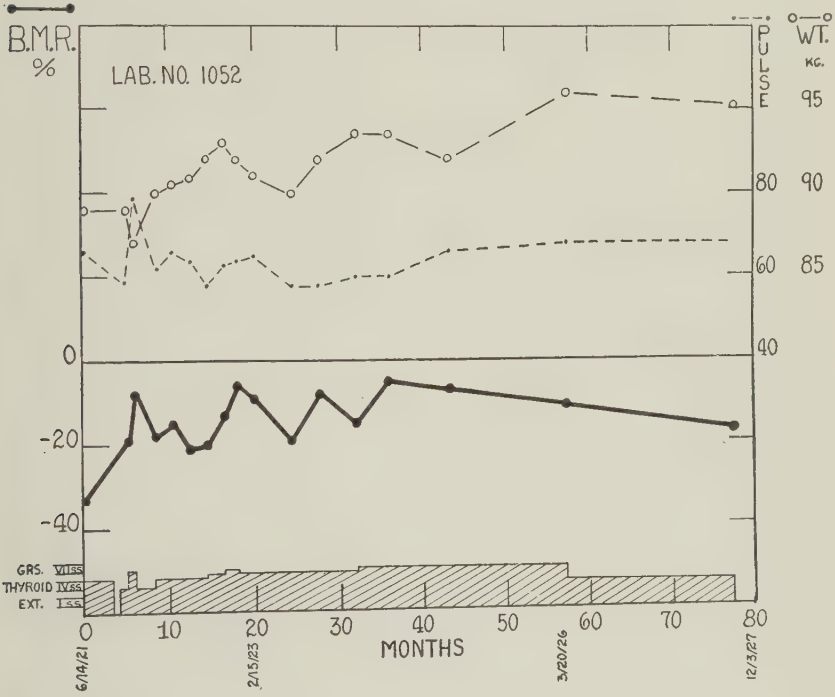

FIGURE 47. *Spontaneous Adult Myxœdema (Case No. 1052).*

pressure 96/74. The temperature was 97°. The urine showed no albumin or sugar, specific gravity 1.029, and the sediment contained a rare hyaline and granular cast. The blood showed 4,400,000 red cells and 80 per cent. hæmoglobin.

Management. — The diagnosis was clearly spontaneous, uncomplicated myxœdema, and thyroid by mouth was begun. The effect on symptoms was prompt, relieving them all and rendering him perfectly well as far as he could observe. The objective manifestations also largely disappeared.

The management of the thyroid dosage and its effect on pulse, weight, and metabolism are shown in the chart. It will be seen that as much as 0.5 gm. (seven and a half grains) a day of Burroughs, Wellcome and Company's thyroid was required to keep his metabolism above minus 10 per cent. On this dosage on several occasions he experienced attacks of sharp precordial pain on effort, which would disappear when the dose was dropped to 0.4 gm. (six grains).

Comment. — This case illustrates the satisfactory management of ordinary myxœdema by giving thyroid gland by mouth. The metabolism data add somewhat to the vividness of our impression, but had these been unobtainable, careful attention to this man's symptoms alone would have served as a satisfactory means of control. Emphasis cannot be laid too strongly upon the precordial pain. This constitutes an absolute indication to decrease the dose of thyroid, regardless of metabolic rate.

The behavior of body weight here is slightly unusual. Ordinarily these patients lose very rapidly; this man gained instead. As his metabolism rose his appetite and food intake did likewise, so no weight loss was apparent. Of course the early weight loss is due to diuresis. As this man was treated in his home, weights were not obtained at the time when this occurred.

One other point of interest is that as his myxœdema symptoms departed, the blood pressure rose to a normal level. On September 8, 1922, it was 148/96. This properly can be interpreted as due to an increased volume of circulation.

Case No. 3797. *Spontaneous Myxœdema in a Man, Complicated by Complete Heart Block; Sudden Death; Autopsy*

History and Examination. — A retired Jewish railway inspector of seventy, father of four children, three of whom were living and well, entered the hospital January 26, 1926. He had had a hard chancre without secondaries when a young man. Twelve years before entry he had developed the classic symptoms of myxœdema for which, since then, he had been treated intermittently with thyroid with some relief, but not with restoration to perfect health. In 1923 at another hospital, so he stated, he had been given so much thyroid that his basal metabolism, he was told, rose from minus 25 per cent. to plus 20 per cent. and definite hyperthyroid symptoms appeared; nervousness, sweating, tachycardia, and palpitation, but no precordial pain. Since that time he had taken no thyroid, and the hypothyroid symptoms had recurred.

Physical examination showed an elderly, slightly obese Jew with a

waxy pallor. The hair of the head was sparse, that of the axillæ, pubes, and rest of the body practically absent. The skin was dry and rough. The heart was slightly enlarged to the left; the sounds were of poor quality, and there was a soft systolic murmur at the apex; the aortic second sound was accentuated. In other respects the examination was not remarkable, except that there was a small cicatrix on the corona of the penis. The pupils and reflexes were normal. There was no enlargement in the neck and no tremor.

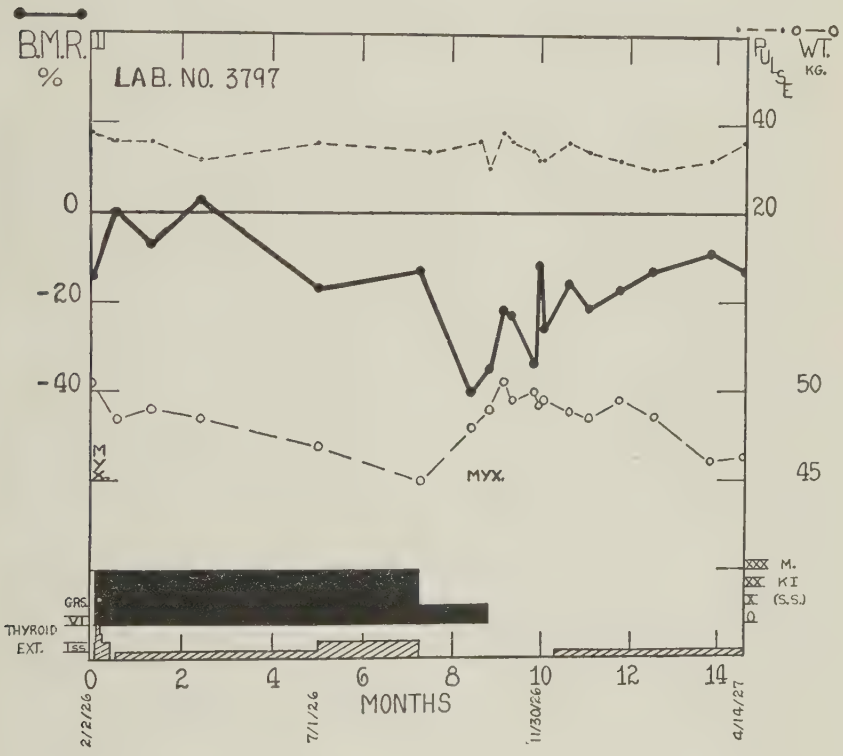

FIGURE 48. *Spontaneous Adult Myxœdema (Case No. 3797).*

The pulse was 37, and in a fortnight's stay in the hospital never rose above 40. The blood pressure was 210/80. Electrocardiogram showed a complete A-V block, flat T_2 wave, and small complexes in all leads. Basal metabolism on February 2, 1926 was minus 14 per cent. The Wassermann on the blood was strongly positive on two occasions.

Management. — The diagnosis of myxœdema was made, also that of

complete heart block probably of syphilitic origin. It was not thought that the two conditions were in any way related; it would seem that the metabolism should have been lower, but as he was a very irregular breather the test may have been inexact. He was put on 0.2 gm. (three grains) of Armour's thyroid per day, also potassium iodide. The former might reasonably have been expected to help his hypothyroid symptoms; it also has been used in heart block. This treatment rather promptly caused the disappearance of his myxœdematous manifestations, and was continued with some variation in dosage, as the chart shows.

On September 10, 1926 thyroid was omitted because he complained of palpitation and forceful heart action. The metabolism promptly fell to minus 40 per cent. and the signs of myxœdema returned, but the patient preferred this status to that while taking thyroid. For that reason he was kept off it until December 12, 1926 when, because he was complaining of weakness, it was again started, this time 0.1 gm. (one and one-half grains) of Armour's daily.

He continued on this dose feeling somewhat better until April 14, 1927, when, following a basal metabolism test, he had a shaking chill and temperature of 101°. He was admitted at once to the hospital and died suddenly while being undressed.

Autopsy. — The autopsy showed an increase in subcutaneous fat which was of normal color. The thyroid was normal in outline but very thin. Its measurements were $2 \times 4 \times 0.2$ cm. On section it was firmer than usual, suggesting muscle tissue rather than glandular in gross appearance. Microscopic examination showed dense bands of connective tissue interlacing through the parenchyma. The follicles tended to be small; many contained no colloid, others varying amounts up to normal. The epithelial cells tended to be small and their cytoplasm was often indistinct.

The heart weighed 330 gm. The myocardium was pale and flabby, the left ventricular wall being 11 mm. thick. There was slight thickening of the intima on the septal border of the left ventricle. The descending branch of the left coronary was calcified and its lumen greatly diminished. The circumflex branch of the left, and the right coronary, showed only small atheromatous plaques without diminution in the lumen. Microscopic sections through the interventricular septum showed a definite fibrosis partly focal, partly diffuse. Numerous large muscle cells in clusters, characteristic of the conduction system, were identified. In at least two places the small patches of fibrosis involved these cells, and one thrombosed vessel was seen.

The aorta showed marked sclerosis in the arch and abdominal por-

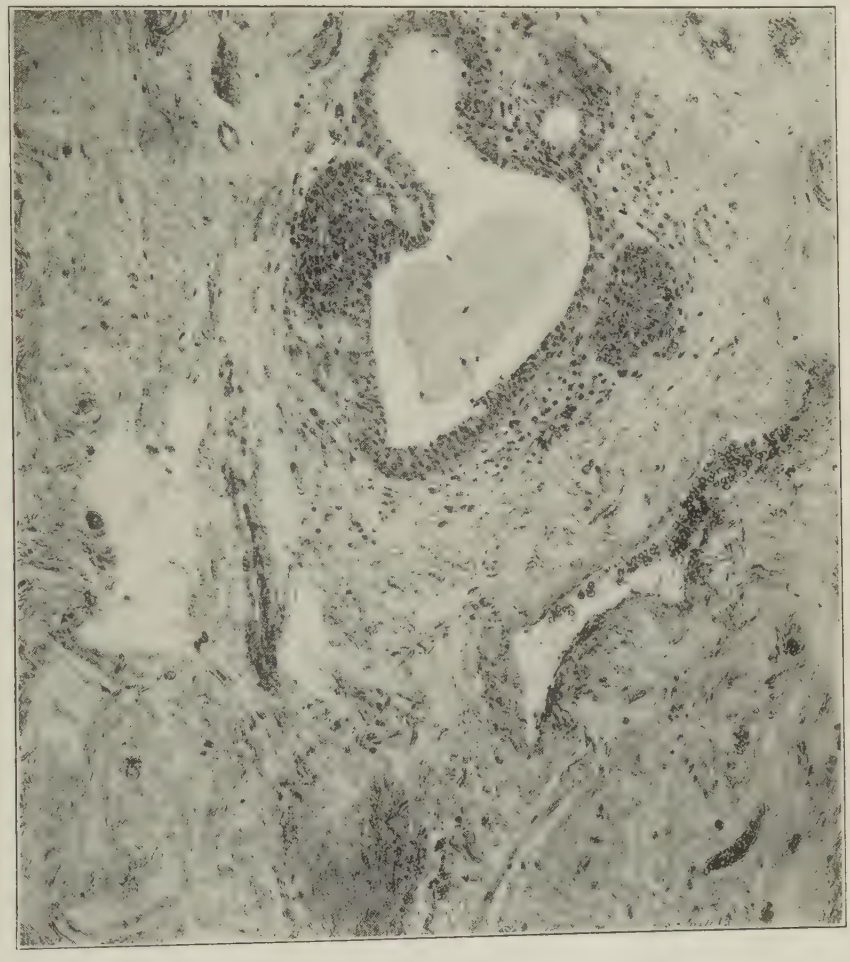

FIGURE 49. *Spontaneous Adult Myxœdema.* Photomicrograph, low power. Note the single follicle in a sea of connective tissue.

Facing page 312.

tions, with calcification and shallow ulceration. Microscopically there was fibrous thickening of the intima, and the adventitia showed two large collections of lymphocytes.

The lungs showed old healed tuberculosis and a recent bronchopneumonia. In other respects the autopsy showed nothing remarkable. The head was not examined.

Comment. — Autopsies on cases of spontaneous myxœdema since the discovery of the specific effect of thyroid have been few and far between. This one therefore is worthy of record for that reason alone. It seems to be a classic one of myxœdema, and the marked atrophy of the thyroid provides adequate explanation of the clinical manifestations. Judging from the histology, one might infer that this gland still possessed some functional capacity. Although the total secretory tissue is clearly greatly reduced, there still remain a few normal looking follicles. Spontaneous myxœdema is probably seldom, if ever, 100 per cent. complete athyreosis; a little tissue capable of function remains, as in this case, and that is one reason why we find so much variation in dosage among different persons with the disease.

The cardiac and aortic condition due to sclerosis might be attributed to the myxœdema since it is believed that that state accelerates sclerotic changes, but the syphilis is a more likely cause. There is no reason to believe that the syphilis affected the thyroid or was causally related to the myxœdema.

Cachexia Strumipriva

This was the term used by Kocher[31] for the condition arising in fourteen per cent. of his first four hundred and eight thyroidectomies for goitre. It was in symptomatology identical with Gull and Ord's myxœdema. It occurred most frequently in those cases in which the operative removal of thyroid tissue had been most extensive. The development of the syndrome undoubtedly is due to the fact that not enough thyroid tissue is left in the body to manufacture the normal requirement of thyroxin. The temporary myxœdema, which we have mentioned under exophthalmic goitre as occurring as a sequel to the latter both in the cases treated surgically and by other means,

is probably not identical with true cachexia strumipriva. The mere fact of temporariness shows that the difficulty is not absence of sufficient thyroid tissue; rather it seems that in those cases for some unknown reason, thyroid activity is temporarily and functionally depressed.

True cachexia strumipriva is seen but seldom nowadays, because operations on the thyroid are planned to prevent it. It is believed generally that total extirpation of the gland in thyroid disease serves no useful purpose, and it is recognized that it entails the risk of accidental removal of the parathyroids, which would of course bring on the serious condition of parathyroid tetany. In spite of this, one recent writer has advocated complete thyroidectomy for exophthalmic goitre, with subsequent thyroid medication to relieve the myxœdema which results; this is advised on the ground that as long as any gland is left the pernicious function of Graves' disease may recur. There is something to be said for the method theoretically; its practical objections, however, are likely to stand in the way of its general adoption.

Of the treatment of cachexia strumipriva, it is unnecessary to speak, since it is identical with that of spontaneous myxœdema.

Cretinism

The cretin, although likewise suffering from athyreosis, is in many respects different from the adult subject with myxœdema, chiefly for the reason that the thyroid lack is effective during the period of growth. The adult with myxœdema, previous to the development of the disease, was a normal person, and an adequate supply of thyroxin will restore him to that status. The cretin, on the contrary, never has been normal, at least not in post-uterine life, and the supply of thyroxin adequate to

elevate his metabolism to a normal level will not make up for all the retarded development that has resulted from the thyroidless period. In other words, if thyroid lack occurs during the growth period, irreparable retardation in development of various organs may result; it is not merely a matter of hypometabolism.

The onset in sporadic cretinism is insidious, and as a rule symptoms begin to appear at about the third month. Regarding this, Talbot[32] says: "An explanation for the delay in the appearance of the symptoms is the possibility that up to the time of birth the fetus receives a supply of thyroid secretion through the placental blood which lasts for an indeterminate time and thus delays the appearance of the symptoms. It is not inconceivable that this is supplemented later by small amounts from the mother's milk". In rare instances, if the mother has been myxœdematous during pregnancy, a child will show the cretinoid characteristics at birth.

As we have pointed out in Chapters I and IV, cretinism, like colloid goitre, is both endemic and sporadic. The endemic cretin sometimes possesses a goitre, sometimes an atrophic thyroid; the sporadic cretin always possesses an atrophic thyroid. The symptomatology of the two forms, endemic and sporadic, is similar, but de Quervain[33] points out that among endemic cretins the developmental retardation is more striking in the cases with atrophic than with goitrous thyroids. The etiology very probably is quite different in the two forms of cretinism.

Endemic cretinism clearly is closely related to endemic goitre. Iodine lack in the first generation or two will produce simply colloid goitre. In the offspring of mothers made goitrous by iodine lack cretinism appears and consequently is due to

inadequate supply of iodine to the fœtus. Marine[34] has shown for animals that goitrous mothers ordinarily giving birth to cretinous offspring will give birth to normal offspring if fed iodine during pregnancy. In contrast to this a sporadic cretin usually is the child of apparently normal parents, and the cause of the failure of the thyroid to develop is entirely obscure. Talbot[35] has studied the metabolism of the mothers of several sporadic cretins without being able to discover any abnormality in it.

The symptoms and signs of both sorts of cretinism are those of adult myxœdema plus those resulting from retarded development and growth. To the description of Fagge, given in Chapter I, there is little to add. The cretin, as it ages, in contrast to the normal child, preserves the bodily proportions of the new-born infant. Thus the head is relatively large and the extremities short. There is dwarfism but often with a trunk length which is not reduced. The belly is very prominent, nearly always with umbilical hernia. The tongue is very large and the mouth held open in consequence, giving a very peculiar facies, better pictured than described. So characteristic is it that it makes all cretins appear as blood relatives. The face is for the most part expressionless, although cretins are capable of a rather comical type of smiling grimace when amused. As in adult myxœdema, the voice is characteristically hoarse.

A form of late cretinism, or juvenile myxœdema, such as that of Fagge's case No. 2 cited in Chapter I, is occasionally encountered. Here, since we are dealing with an acquired disease, the picture is modified from that of true congenital, infantile cretinism by the extent of the normal growth and development which has preceded the onset of the cretinism or myxœdema.

Diagnosis

After the syndrome is developed, diagnosis is not difficult; the characteristic appearance is sufficient. The degree can be reckoned from the mentality. As Talbot has emphasized well, the important thing is to make the diagnosis before the classic picture is established. As an aid in doing this he lays stress on a heavy expression and pig-like appearance of the eyes. A lemon yellow tint appears early on the mesial aspect of the cheeks disappearing when the child cries. Changes in the tone of the voice always are important.

Whenever an infant displays any of these characteristics, cretinism should be suspected, even though the more well recognized manifestations have not appeared. In proving the diagnosis basal metabolism determinations are invaluable, for after the age of three months, and perhaps sometimes earlier, the cretin, like the adult with myxœdema, shows a lowered basal metabolism.

Treatment

Treatment should be started as soon as the diagnosis is made or even strongly suspected, for the reason that time is very precious in the early stages of the disease. The end result is of course going to be related importantly not only to the actual degree of athyreosis, but also to the age at which treatment is started. Talbot[32], again, says: "The growth of the infant's brain is very rapid, and, at the end of the first year, it is two and one-half times the original size. This is also the period of greatest proportional growth of the rest of the body. If the failure to obtain complete mental restoration can be traced to the absence of thyroid secretion during this period of rapid growth,

and if the thyroid gland supplies a necessary substance for complete development of the brain cells, then the importance of an early recognition of cretinism cannot be overemphasized." Furthermore, Talbot insists on the importance of obtaining a photograph before treatment is begun, and if possible a metabolism determination, of every baby suspected of having cretinism. On thyroid the cretinous child rapidly becomes normal in every way. Were there no proof of its having been cretinous, a subsequent physician might doubt the diagnosis and stop the treatment at a time when so doing would be disastrous.

The treatment of cretinism may be divided into two categories; that of the infant or young child cretin, and that of the older child or adult cretin. Cretins twenty or more years old are occasionally met, who have never had any or only irregular and scanty treatment with thyroid. Their mentality, as we have said, varies with the degree of athyreosis. Treatment may bring about some improvement, but usually not very much, and sometimes none. Means and Aub[7] reported observations on a patient twenty years of age with very mild cretinism, whose metabolism could be varied from minus 23 per cent. to plus 10 per cent. or more by an initial dose of 1.6 gm. (twenty-five and one-half grains) of thyroid given during a week, and maintained by a daily ration of 0.1 gm. (one and one-half grains) of thyroid (Burroughs, Wellcome and Company). There was not much change in her mental status as a result of this, but fat pads which had been present over her back disappeared, and her skin became warmer and moister. After fifteen months of treatment, during which time she grew 2 cm., she gave up the treatment as not conferring enough benefit to be worth the bother.

Du Bois[6] has studied a man of about thirty-six with a much more severe grade of cretinism, whose metabolism averaged 20

per cent. below that of adults of his age, and 50 per cent. below that of children of his size. On thyroid sufficient to raise his metabolic level to the normal adult standard, he developed a tachycardia and felt sick and miserable. There was also a story that during a period of fifteen years courses of thyroid (Parke, Davis and Company) had been tried, but that on doses no bigger than .03 to 0.2 gm. (one-half grain to three grains) a day the patient would develop tachycardia and weakness and often syncope.

A great many cretins are cared for at the Walter E. Fernald State School for Feeble Minded Children, and one of us recalls very clearly hearing Dr. Fernald remark some years ago that in his experience the treatment of older cretins with thyroid had been in the main disappointing. The intellectual improvement was very slight, and toxic symptoms were produced readily. It seems to be the case with cretins, as we noted earlier in adults with myxœdema, that they are more susceptible to enteral hyperthyroidism than normal persons, possibly because the thyroid of normal individuals can in a measure store excess thyroxin and protect the subject from an excess in the blood stream, whereas the cretin, having little or no thyroid tissue, lacks this safety device.

In many instances the degree of actual hypothyroidism seems slight; certainly so, as compared with the often complete or nearly complete athyreosis of persons acquiring myxœdema during adult life. The somatic manifestations, therefore, dry and coarse skin, thick tongue, etc., etc., are sometimes not so well marked in the older cretin as in adult myxœdema and do not require treatment per se. The difficulty with the older cretin is not his hypothyroidism but the development defects, especially of the brain, resulting from the hypothyroidism

from which he suffered in the growth period. These last are irremediable.

In general it may be said that with the older cretins thyroid may be given cautiously in small doses and may confer a little benefit, but if it does not do so, and particularly if it does obvious harm, it should be abandoned.

In sharp contrast to this stands the therapy of infant cretins. In them early diagnosis and prompt, proper and sustained treatment may make the difference between normal progressive development and imbecility. A heavy responsibility rests on the doctor to recognize and treat these cases early. When the mother is goitrous, he may be watching for signs of cretinism in the child; sporadic cases he will only pick up by general watchfulness and attention to everything the mother says about the infant's behavior.

Talbot finds that all untreated cretins are short for their age, the deviation being the greater, the older the child. Growth usually will take place when sufficient thyroid is given to bring the basal metabolism up to what would be expected for the age. In the early years of life this growth may reach and remain at the normal rate.

Infant cretins require relatively much larger amounts of thyroid to bring metabolism to a normal level than adults with myxœdema. The dosage required at different ages in terms of U. S. P. thyroid has been found to be roughly as follows:

Age	*Dosage*		
2–4 months	6 mgm.	($\frac{1}{10}$ grain)	daily
4–8 "	12 mgm.	($\frac{1}{6}$ ")	"
8–12 "	18 mgm.	($\frac{3}{10}$ ")	"
12–24 "	26 to 48 mgm.	($\frac{2}{5}-\frac{3}{4}$ ")	"
2–4 years	0.03 to 0.1 gm.	($\frac{1}{2}-1\frac{1}{2}$ ")	"
4–12 "	0.64 to 0.2 gm.	(1–3 ")	"

FIGURE 50. *Sporadic Infantile Cretinism* (*Case No. 262156 M. G. H.*). (Courtesy of Dr. F. B. Talbot.)

Facing page 321.

After the child attains a normal status the dose often can be reduced.

A final word should be said on the prophylaxis of cretinism, particularly in goitrous districts. All women exhibiting any thyroid fullness during pregnancy should be given small doses of iodine, 10 mgm. per week, and those showing the slightest evidence of hypothyroidism should be given thyroid. There is no question that, if this policy is rigidly carried out, fewer cretins will be born.

CASE NO. 262156. *Sporadic Infant Cretinism*

The infant shown in Fig. 50, thirteen weeks old at the time, was born at full term, with normal delivery, and had a birth weight of seven and one-half pounds. He had been breast fed since birth. As one may see at a glance, the picture is typical of cretinism: the forehead was wrinkled, the hair line low, the eyes pig-like, the nose nearly bridgeless, the tongue thick and protruding, the neck short, the abdomen prominent with umbilical hernia; there was a yellow tint to the face and hoarse, thick voice. The skin and hair were not noticeably coarse in texture; otherwise the syndrome was complete.

The laboratory findings of interest were a slight secondary anæmia and a low potential and T_2 wave in the electrocardiogram.

He lost these manifestations on thyroid and developed normally for a time. Later he acquired rheumatic heart disease and died at the age of three.

CASE NO. 4302. *An Adult Sporadic, Male Cretin Developing Adenomatous Goitre*

History. — The patient was first seen at the Massachusetts General Hospital clinic in October, 1926, at which time he was twenty-one years old. He was said to have weighed eleven pounds at birth. In early infancy he was pale, pot-bellied, dry-skinned and very indifferent about food; he had to be wakened to be fed. At six months he had been recognized as a cretin and started on thyroid. On this he rapidly assumed an apparently normal status, and with gradually increasing doses developed in a more or less satisfactory fashion thereafter. He never was entirely normal in that the pot belly remained, and he was slow in

attaining his locomotor function; he could not sit up until two and one-half years of age nor walk until four and one-half.

At the age of thirteen thyroid had been omitted for eight months, and after three of these he had developed thick speech, dry skin, coarse hair, weakness, stupid appearance and mental retardation. Upon the renewal of thyroid these promptly disappeared.

Two years before his first visit to the clinic he had rather suddenly required a No. 15 collar instead of a No. 14, and six months later a definite swelling in the left side of his neck had been observed. It is interesting to note that coincident with the appearance of this mass the dose of thyroid had been reduced from the customary 0.3 to 0.12 gm. (five to two grains) daily, and later to 60 mgm. (one grain), because the school physician had found that his heart was beating too rapidly.

Examination. — Examination on November 3, 1926 showed a fairly well developed and nourished young man with somewhat expressionless face and evident stupidity. The legs were slightly short and the abdomen slightly prominent. The hair and skin were somewhat dry. His gait was a little uncertain. In the left lobe and isthmus of the thyroid there was a hard, firm, rounded tumor, the size of a lemon. It dipped down beneath the clavicle, but the lower pole could be felt on swallowing. The dose of thyroid in the six months preceding this examination had been 60 mgm. (one grain) daily. The basal metabolism was minus 23 per cent.

Management. – In order to size up the situation thyroid was omitted for a little over two months. The metabolism slowly dropped as the chart shows, and the weight increased. After three weeks off thyroid he began to show increased mental retardation, and after six he had backache and pains and cramps in the legs. At this time also his gait became more uncertain; he felt weak, and his speech became thick and his face puffy. His skin became dry, and his beard grew less rapidly. After eight weeks off thyroid his hearing became poor and his bowels very constipated. He was irritable and slept poorly. There was occasional vomiting.

On January 12, 1927, Armour's thyroid 30 mgm. (one-half a grain) three times a day was begun. Within ten days the symptoms disappeared. His mentality returned to its usual state, his hearing improved, and his beard resumed its normal rate of growth.

From this he went on in February, 1927 to a definite thyrotoxic state. He became unusually active; the pains in the legs stopped, and precordial twinges began. He talked fast, was restless and irritable and had frequent crying spells. The metabolism and pulse both assumed a supernormal rate. At this time, March 8, 1927, it was noted that the goitre had shrunk to half its previous size.

The dose of thyroid was reduced to 30 mgm. (one-half a grain) daily, and on this the thyrotoxic symptoms improved, and the metabolism and pulse fell to normal levels. The goitre continued to grow smaller until on October 10, 1927 the nodule was no bigger than a large pea. At this time

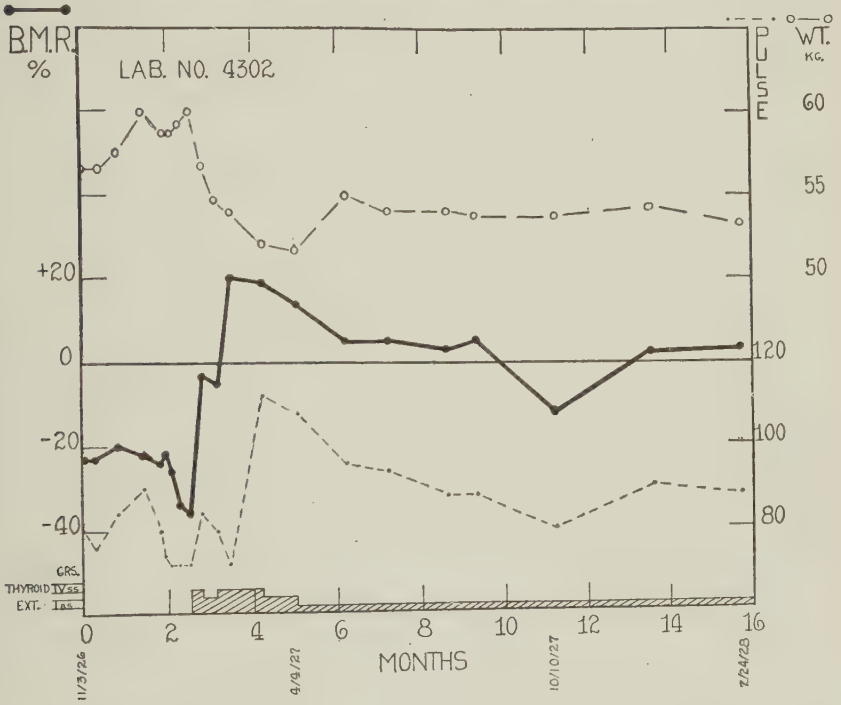

FIGURE 51. *Adult Cretin Developing Adenomatous Goitre (Case No. 4302).*

the metabolism was minus 12 per cent., and he was freer of symptoms than he had ever been.

Comment. — This case illustrates a number of important points. We can observe the late results in the treated cretin. We suspect that during the growth period the treatment was not entirely adequate. Omission of thyroid is followed by the development of typical myxœdema, which promptly disappears on resuming thyroid. Several noteworthy symptoms are illustrated; the deafness, the constipation, the retarded growth of hair, and the pains and cramps characteristic of hypothyroidism.

The most striking feature, however, is the thyroid adenoma, and the diminution in thyroid requirement which occurred at the time it developed. Then, too, the decrease in size of the tumor later, when thyroid was recommended after a period without it, is of distinct interest.

One is led to speculate whether the development of this adenoma represents an attempt on the part of nature to cure the hypothyroidism. Certainly it alone could not supply an adequate quantity of thyroxin, but it may have supplied a portion, which is the reason the dose necessary for maintenance fell. Later on, when an unnecessarily large dose is given, the adenoma in turn involutes. It is furthermore remarkably interesting that the sporadic cretin has sufficient vestige of thyroid tissue left to grow an adenoma at all.

This cretin, like many others, is readily rendered thyrotoxic by excessive doses of thyroid, a point of considerable practical importance.

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CHAPTER IX

MALIGNANT TUMORS AND INFLAMMATIONS OF THE THYROID

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Malignant Tumors

Malignant disease of the thyroid is not a condition of great rarity. The possibility of its occurrence always should be borne in mind in dealing with thyroid enlargements, particularly at or beyond middle life. Since effective treatment depends upon prompt diagnosis, the early recognition of evidences of malignancy becomes of extreme importance, as well as a knowledge

of the type of goitre in which this change is most prone to occur.

Occurrence

Wilson[1] states that malignancy of the thyroid occurs in this country once in every 928 autopsies. While it seems probable that carcinoma of the thyroid develops more frequently in endemic goitre regions, this supposition can not be confirmed as yet by statistical data. Pemberton[2] states that the relative frequency of malignant tumors of the thyroid occurring in the Mayo Clinic from 1910 to 1926 was 2.7 per cent. with reference to adenomatous and colloid goitre, and 1.66 per cent. with reference to all goitres, including exophthalmic. Speese and Brown[3] give the incidence of malignancy as 4.6 per cent., Walton[4] as 3.2 per cent., and Graham[5] as between 1 and 2 per cent. of thyroid specimens received in the laboratory from the Surgical Division of the Lakeside Hospital in Cleveland.

In our clinic from 1920 to 1927 inclusive 3.5 per cent. of goitres operated on were classed as malignant. In general it would seem fair to say that malignancy may be expected in about two per cent. of goitres removed at operation. From sixty to seventy per cent. occur in females. While malignancy may be found at an early age, it is most frequent in the fourth, fifth, and sixth decades. The most significant etiologic factor is the tendency of malignancy of the thyroid to develop in pre-existing goitres.

Pathology

Since the presence or absence of malignancy in the thyroid can not be judged by the same histologic criteria as malignancy of other organs, there has been a great deal of confusion in

regard to tumors of the thyroid. Not infrequently the evidence of malignancy is clinical rather than microscopic, as shown by a tendency to recur locally, to invade, or to metastasize through the blood stream. On this account, a satisfactory classification has proved difficult, particularly since the various types of thyroid malignancy appear to merge into one another.

The great majority of malignant tumors of the thyroid are epithelial in origin. While in the past thyroid tumors interpreted as sarcoma have been frequent in the literature, there is a growing tendency to believe that most of these so-called sarcomata are actually carcinomata. Thus Ewing[6] states that the mesoblastic origin of most of the sarcomata reported in the literature is highly improbable, and that the occurrence of true sarcoma of the thyroid in man still requires demonstration. In any case, thyroid tumors considered to be sarcoma are apt to show evidence of a high degree of malignancy and in general lead rapidly to death from invasion or metastasis.

The malignant epithelial tumors of the thyroid belong for the most part under the general heading of adenocarcinoma. A few tumors show solid masses of epithelial cells, leading to a diagnosis of carcinoma, but in general the tendency to form alveoli is maintained, so that there is no sharp dividing line between adenocarcinoma and carcinoma. Occasionally a dense constricting scirrhous type of growth may occur in the thyroid as in other organs. For a detailed classification of cancer of the thyroid, the reader is referred to papers by Langhans[7], Kocher[8], and Ewing[6].

Certain types require particular mention. The chief in importance and frequency is the malignant adenoma, the "wuchernde Struma" of Langhans[7]. These tumors are encapsulated nodules at times reaching a considerable size, and show-

ing evidence of unicentric origin and peripheral growth in that the youngest alveoli appear in the outer zone, while nearer to the centre, colloid-containing follicles of more adult type often are found. The microscopic picture is extraordinarily varied, and separation from benign encapsulated adenoma, particularly of the fœtal type, is difficult. Another group shows a definite papillary structure, sometimes observable in gross section as feathery projections into cystic cavities. Here a differentiation from benign adenomata of similar type may be difficult, but rests on the ordinary evidences of malignancy.

Tumors arising in the thyroid or in close relation to it, but usually ascribed in origin to some other structure, occur rarely. Here belong malignancy arising from the parathyroid, from the post-branchial body, and occasional cases of squamous cell carcinoma attributable to epithelium displaced in the course of thyroid development. Other tumors may be very difficult to differentiate clinically from thyroid malignancy, such as occasional cases of lymphosarcoma or branchiogenic carcinoma developing low in the neck.

In malignant adenoma, the morphologic picture is so varied that it is unsatisfactory evidence of the presence or absence of clinical malignancy. Graham[5] states that all conceivable steps, stages and degrees in the growth, differentiation and degeneration of fœtal, intermediate and colloid adenoma may present themselves for interpretation, and that it makes very little practical difference what the tumor looks like under the microscope. He believes that the existence of malignancy should be evidence of invasion, and that the most constant single indication of malignancy is invasion of the blood vessels. Epithelial tumors that are encapsulated and show no invasion of the blood vessels are benign, irrespective of their microscopic appearance

otherwise. This statement was borne out by the clinical course of the cases traced following operation. The reliability of this criterion has been confirmed by Warren[29]. Blood vessel invasion constitutes an adequate standard for malignancy.

This question is closely associated with instances reported in the literature as metastasizing colloid goitre, or metastasis from the normal thyroid. While cases showing metastasis of apparently normal thyroid tissue occur, conclusive evidence of the benign character of the thyroid is lacking. Ewing[6] states that the natural tendency of the metastatic cells to develop into normal thyroid tissue may alter progressively the structure of a secondary growth, so that an original carcinomatous area may eventually appear adenomatous. Simpson[9] reports three cases of thyroid metastasis to bone which after removal showed typical thyroid tissue. All these patients later developed unmistakable clinical evidence of malignancy of the thyroid gland and died within a year and a half following operation. He believes that there is no such entity as benign metastasizing goitre and that this term should be abandoned. Graham[5] would include such cases under the general term of carcinoma. From a clinical point of view there seems little doubt that they should be classed as malignant.

Extension from malignant growths of the thyroid may take place by direct invasion of contiguous structures, particularly the adjacent fascial planes and overlying muscles; by invasion through the lymphatics, in which progression occurs downward along the jugular plexus or inferior thyroid vessels toward the mediastinum, upward toward the submaxillary nodes, or posteriorly to the region between the trachea and œsophagus; or by metastasis through the blood stream. In general, carcinoma developing diffusely in the thyroid progresses by direct and

lymphatic extension, while encapsulated malignant adenomata metastasize through the blood stream until rupture of the capsule occurs, after which they invade in a similar manner. Papillary and scirrhous adenocarcinoma are primary lymphatic invaders (Graham)[5].

Metastasis occurs principally to the regional nodes, and next in frequency to the lungs and mediastinum. A striking feature is the tendency to bone metastasis, an occurrence only exceeded in percentage of incidence in carcinoma of the breast or prostate. Occasionally such a metastasis apparently remains single over a considerable period of time. The capacity of metastases to perform thyroid function has been discussed frequently, but can not be said as yet to be fully demonstrated.

The development of malignancy of the thyroid in preëxisting goitre is of great practical importance. While this relationship long has been observed, its significance is being increasingly appreciated. The great majority of carcinomata of the thyroid develop in glands which have been the seat of adenomatous change, particularly those containing adenomata of the fœtal type. In the hyperplasia associated with exophthalmic goitre, the development of carcinoma is very rare. Herbst[10] states that in the Mayo Clinic no instance of carcinoma occurred among 2667 cases of exophthalmic goitre. Malignant change should be considered a possibility in non-toxic nodular goitre. It is negligible in toxic goitre. Hyperthyroidism is seldom, if ever, associated with malignancy.

The actual percentage figures of cancer of the thyroid having their origin in previous goitres vary somewhat, with a tendency to higher rates in recent statistics, where the association is more closely looked for. Müller and Speese[11] give the percentage of cases in which malignancy was preceded by goitre

as 59, Speese and Brown[3] as 78.5. Graham[5], on the basis of pathologic examination, found that over 90 per cent. of carcinomata had their origin in preëxisting adenomata. Pemberton[2] states that 80 per cent. of 274 cases operated on for carcinoma of the thyroid gave a definite history of preëxisting goitre for two years or longer, while in an additional 7 per cent. the specimen showed unmistakable evidence of carcinoma arising in fœtal adenoma. In our small series, developing for the most part in a non-goitrous district, a goitre was noticed by the patient four years or more before operation in half the cases. For an example see Case No. 4463, page 341. The long duration of the primary goitre in many instances is noteworthy. Thus its average duration in Speese and Brown's[3] cases was 12.6 and in Pemberton's[2] 13.8 years.

The actual probability of the development of carcinoma in a patient with adenomatous goitre can not be stated. Nearly every patient with carcinoma of the thyroid comes sooner or later to a hospital clinic, while those with adenomatous glands may carry them through life without medical attention, a situation which may tend to exaggerate the incidence of malignancy. While operation should be advised in patients over thirty having adenomata of the thyroid of appreciable size, it does not seem fair to the patient to stress too much the possibility of cancer, since that idea may produce a lasting impression unjustified by the actual risk. This argument should be reserved for those cases in which operation is important on other grounds or in which some suspicion of malignancy exists. Nor can we say that we influence very greatly the incidence of malignancy except in those cases where discrete adenomata can be removed, leaving normal thyroid tissue to maintain function.

Clinical Course

Malignancy of the thyroid may present itself clinically, as pointed out by Walton[4], in three general types. The largest and most important consists of those cases in which malignancy is secondary to previous goitre. A second group, perhaps relatively commoner in non-goitrous districts, is made up of those cases where the thyroid enlargement is apparently malignant from the onset (see Case No. 5382, page 343). In a much smaller group the primary thyroid lesion, insignificant or unrecognizable, is overshadowed by actively growing metastases (occasionally single) elsewhere in the body (see Case No. 288536, page 344).

The duration of the disease varies greatly. Occasionally it runs a fulminating course, leading to a fatal outcome within a few months after the discovery of a tumor (Case No. 5382, page 343). At times the disease progresses very slowly, particularly if of the papillary type of adenocarcinoma, showing a tendency to local recurrence after operation, but little in the way of invasive properties. The majority of cases have an intermediate rate of development. Death may occur from general dissemination or from the effects of local pressure on the trachea or œsophagus, to which occasionally may be added those of ulceration and hæmorrhage. The late stages often are rendered peculiarly distressing from increasing respiratory obstruction.

Diagnosis

The essential thing in diagnosis is recognition at the earliest stage possible. The actual type of tumor present is of minor importance and can not be recognized clinically. Emphasis should be laid therefore on the incipient signs of malignancy, while the tumor still may be encapsulated, rather than on those

which develop when invasion beyond the thyroid occurs. The early signs may be slight or absent; if the diagnosis is obvious on examination of the local tumor, the disease has progressed in many cases beyond cure by operation. Frequently the diagnosis is made only on pathologic examination after an operation for supposed adenomatous goitre. Balfour[12] found that in only 18 per cent. of a series of 103 cases of cancer of the thyroid could a positive clinical diagnosis of cancer be made; in an additional 36 per cent. malignancy was considered a possibility, while in 46 per cent. the condition was not even suspected. These findings serve to emphasize the desirability of operation for a nodular goitre in patients approaching middle life.

The most significant early change is steady or rapid progression in the size of the thyroid tumor. The great majority of benign nodular enlargements of the thyroid in people of cancer age increase so slowly that no change in size is appreciable, except over long periods of time. Such tumors may even regress. Exception occasionally occurs in the way of hæmorrhage into a degenerative cyst, which is accompanied by a sudden enlargement, subsequently diminishing, a history sufficiently characteristic so that the true situation is not in doubt. Steady or rapid increase in size of a goitre in people beyond thirty, particularly if accompanied by increased firmness of the tumor, which need not be of a stony hardness, is suggestive evidence of the development of malignancy.

The probability of malignancy is increased by the occurrence of hoarseness or aphonia, due to recurrent laryngeal nerve paralysis from pressure or invasion before compensation has had time to develop. Although paralysis is significant when it occurs, the majority of cases do not show this change. Fixation of the

tumor to adjacent structures, particularly to the overlying muscles, and possibly to the skin, is the most definite sign of malignancy. When one is examining for this point, it is well to test the movability of the tissues overlying the gland as well as that of the gland itself. Fixation may be more apparent on attempted motion in a vertical rather than in a lateral direction. Increased vascularity, as well as dilatation of the overlying veins, sometimes may be made out. A feeling of pressure in the neck, or later, an actual obstruction to respiration or to swallowing may develop. While these symptoms may occur in benign enlargements, it should be noted that they are then better accounted for by the actual size or situation of the tumor than is the case with malignancy. Pain is a late symptom. In advanced cases, local or distant metastases may be found.

The diagnosis rests on the history and physical examination. Little aid is given by special methods of diagnosis. The basal metabolism is ordinarily within normal limits, but may be elevated, or in rare instances below normal. The X-ray is of principal value in detecting metastases, which are most commonly found within the thorax, but should be looked for in the skull, sternum, spine and long bones.

Differential Diagnosis

The principal distinction necessary is between benign and malignant tumors of the thyroid. This question has been discussed already. More rarely it may lie between inflammatory changes in the thyroid and malignancy. Inflammation may lead to increased induration and to fixation by adhesions, which may be difficult to distinguish from the infiltration of malignant disease, provided that the change is not sufficiently acute to lead to local or constitutional signs of infection. Con-

fusion may occur in diffuse chronic thyroiditis, or in adenomatous and cystic goitre, where mild infection occurs in certain areas of the gland. In the former case the enlargement of the gland is symmetrical, moderate in degree, and may be extremely hard, but of a more uniform consistency than is likely with cancer. Change in size is very slow and atrophy may take place instead of progression. At times the distinction between chronic thyroiditis and malignancy can not be made without operation. Cystic goitres with infection may simulate malignancy very closely. However, there may be a story of increase in size accompanied by tenderness and signs of inflammation, with later subsidence of acute symptoms, leaving induration and infiltration. Other tumors of the neck, for the most part malignant, may develop in such close relation that separation from thyroid tumors is difficult or impossible. Thus certain cases of carcinoma, originating either in branchial rests or metastatic from other structures, may be impossible to differentiate from thyroid tumors, as may occasional cases of Hodgkin's disease, or lymphosarcoma. This separation is relatively unimportant since in any case the treatment must be by operation or radiation, depending on the characteristics of the tumor. What is important is to urge operation in every goitre which by its behavior leads to suspicion that it may be malignant.

Treatment

Operation. — The treatment indicated depends on the stage of the growth when first seen. In cases where malignancy is only suspected, or where, if diagnosed, the disease is essentially limited to the gland without demonstrable evidence of invasion of the surrounding tissues, it is primarily surgical. In such cases the disease usually is confined to one part of the gland, so

that complete removal of the affected lobe including its posterior capsule is sufficient. Occasionally an adenoma after removal is found to be malignant, and the question comes up as to further treatment. Herbst[10] states that the experience of the Mayo Clinic goes to show that enucleation of a malignant adenoma, if undertaken before rupture of the capsule has occurred, is an adequate operation. Where the disease has affected both lobes of the thyroid, infiltration of the adjacent tissues usually has developed; this may take place while the disease involves one lobe only. These are the cases in which a definite clinical diagnosis can be made without operation. No general rule for treatment can be laid down; it is a question of individual judgment depending on the case, influenced particularly by the degree of fixation of the thyroid. If an apparently complete removal can be carried out by sacrificing the overlying muscles and other non-essential structures, the patient is probably better off with operation followed by X-ray than he would be with radiation alone, particularly if respiratory obstruction is threatened. When the growth proves irremovable, benefit may be expected from the direct implantation of radium needles or seeds. In many cases when first seen the growth is so fixed and has extended so obviously to important structures that it is clear that operation would do more harm than good, and here it is a question of radiation alone. In the late stages of the disease, indirect palliative procedures may become necessary, such as tracheotomy or gastrostomy for feeding.

Radiation. — Certain types of tumors of the thyroid are especially sensitive to radiation, such as papillary adenocarcinoma, lymphoma-like tumors and adenocarcinoma. Rapidly growing lymphosarcomata of the thyroid sometimes respond with startling rapidity to irradiation. They may even disappear altogether

only to recur in a short time in a form far less amenable to treatment. In general, metastases are less responsive to radiation than the primary tumor. Craver[14] states that of 33 cases treated by radiation at the Memorial Hospital, New York, 10 were living at the time of his report. Of these 9 had an operative removal of the tumor, which in 7 cases was apparently complete. Of 13 cases not operated upon, 11 had died, and of these 3 had shown temporary improvement, while 8 were unimproved. Portmann[15] reports distinctly better results from the combination of radiation and surgery than from surgery alone. However, of 22 cases treated solely by radiation 25 per cent. were alive, although none of these longer than two or three years. More favorable results are reported by Pfahler[16]. While it is true that those treated by radiation alone are likely to be advanced and unfavorable cases, nevertheless this form of treatment is not sufficiently promising to replace operation where it can be undertaken. We may expect in many cases, however, lessening of activity of growth, symptomatic relief with improvement in general condition, and prolongation of life. While surgery should be taken as the method of choice, the efficiency of this form of treatment is increased by radiation at suitable intervals after convalescence.

Prognosis

While malignancy of the thyroid bears deservedly unfavorable reputation, even in comparison with carcinoma of other organs, this view is not entirely borne out by the facts. In few other regions can prophylaxis be carried out so readily and so efficiently, as by the removal of adenomatous nodules from the thyroid; however, by the time the diagnosis of malignancy can be made clinically, radical cure often is impossible. The prognosis varies in the individual case, depending chiefly upon

the stage at which treatment is undertaken, but also upon the type of tumor and its degree of malignancy. The most favorable cases are those in which operation is carried out before clinical malignancy can be recognized. Such cases are most commonly malignant adenomata, in which operation is undertaken under the diagnosis of benign adenoma, at a time when the tumor is still encapsulated. Removal under these conditions results commonly in complete and permanent extirpation of the local tumor, although distant metastases may have occurred already through the blood stream. Where the growth is so far advanced as to lead to a definite diagnosis of malignancy, the situation is by no means hopeless, provided the tumor can be removed at operation. In this connection Herbst[10] states that 27 per cent. of patients with non-encapsulated tumors reported free from recurrence, as against 47 per cent. with encapsulated tumors, while Pemberton[2] found that a third of the cases in which carcinoma was diagnosed or suspected were alive three years after operation.

With regard to the type of growth, diffuse carcinoma in general is the most malignant, and papillary adenocarcinoma the least malignant form in which cancer of the thyroid occurs, malignant adenomata occupying an intermediate position. Pemberton[2], reporting the results of operation (in most cases combined with radiation) at the Mayo Clinic, found 21 per cent. of the patients with diffuse carcinoma were alive three years later, as compared with 38.7 per cent. of those with malignant adenoma, and 48 per cent. of those with papillary adenocarcinoma. To such operable cases must be added a varying proportion, perhaps another third, in which the extent of invasion found on examination makes complete removal technically impossible. Under these conditions operation is rarely advis-

able, and the chief reliance must be placed on radiation. While cure is naturally not to be expected under these conditions, occasional cases will show definite benefit.

CASE NO. 4463. *Benign Growth of Twenty Years' Standing: Prophylactic Operation Withheld: Later Development of Malignancy.*

History. — A widowed laundress of 58 entered the hospital February 4, 1927, with the following story: In August 1909, she was sent into the hospital on account of a lump in the thyroid region of four years' duration, which on account of recent enlargement and increase in firmness raised the question of malignancy. There were no toxic symptoms. A surgical consultant considered the tumor benign, and the patient was discharged without operation. Following this she remained well until seven months before entry, when a diplopia developed. Two weeks before entry pain in the right eye and forehead above began, at first lancinating, later continuous and severe, and accompanied by lacrimation. She had not been conscious of any change in the thyroid tumor which although persistent had caused no discomfort.

Examination. — This showed a firm enlargement of the right lobe and isthmus, somewhat fixed to the surrounding tissues, extending low and displacing the trachea to the left. There was internal strabismus of the right eye, an absent corneal reflex, and numbness of the right side of the forehead and to less extent of the right cheek. The patient appeared in fair general health. X-rays of the skull, chest, and long bones were negative for metastases. The vocal cords showed normal excursion. The basal metabolism was within normal limits; the spinal fluid negative. The diagnosis was made of malignancy of the thyroid with metastasis causing involvement of the sixth and upper branch of the fifth cranial nerves. Since no other metastasis could be demonstrated and it appeared that the tumor of the thyroid would shortly cause troublesome pressure, operation was advised.

Management.— On February 15, 1927, the right lobe and isthmus of the thyroid were removed. The muscles appeared infiltrated by malignancy near the upper pole. The pathologic report was as follows: "Three spherical, apparently encapsulated nodules, the largest the size of a tennis ball, measuring 5.8 cm. in greatest diameter, the smallest measuring 4.5 cm. On section they show reddish gray surfaces and areas of calcification. Microscopic examination shows a structure of small, closely set follicles lined by hyperplastic epithelium which in places forms multiple layers

with occasional papillary ingrowths. There are areas where the follicles are separated by strands of small undifferentiated cells which show occasional mitotic figures. These areas suggest either a sarcomatous degeneration of the stroma or an overgrowth of undifferentiated epithelium. The growth is malignant and should probably be classed as *sarcoma.*"

The patient made a good convalescence, aside from continuation of her pain and was discharged on March 3. Two weeks later she reentered, and the posterior root of the fifth nerve was sectioned under local anæsthesia. This caused relief of the pain about the eye, but some pain persisted on the right in front of the ear and along the mandible. However, a facial palsy followed the operation, leading to corneal ulceration, which required suture of the lids. The paralysis gradually cleared up, with healing of the eye. The pain was considerably improved. Seven months later, after two series of X-ray treatments, there was a slow recurrence of the growth locally in the neck.

Comment.— This case illustrates the development of malignancy and also the difficulty of determining pathologically the actual type of growth in a long-standing thyroid enlargement. It seems reasonable to suppose that a prophylactic operation at her first admission would have obviated the distressing condition which arose later. At the time thyroidectomy was undertaken, it is doubtful whether it was of any real benefit.

Case No. 2772. *Carcinoma of the Thyroid Simulating Benign Adenoma.*

History.— A housewife of 44 entered the hospital June 22, 1925, with a swelling of the left side of the neck which had been present for four years. It had increased steadily in size and recently caused some discomfort from pressure and cough. Otherwise she was in good health, and showed no evidence of thyroid toxæmia.

Examination. — This was negative aside from an enlargement of the left lobe of the thyroid of a soft and uniform consistency, extending somewhat across the median line and well down into the sternal notch. The basal metabolic rate was plus 1 per cent.

Management.— The condition was considered to be a benign adenoma of the thyroid, and the left lobe of the thyroid except for its posterior part was removed with the tumor. The pathologic report was as follows: "A solid, spherical, apparently encapsulated tumor about the size of a tennis ball. On section it shows a smooth, pale yellow periphery, and a

fibrous, purplish-red centre. A microscopic examination shows a richly cellular, vascular new growth composed of atypical epithelial cells arranged in solid columns, bounded by small blood vessels. The cells are variable, do not differentiate into follicles, and show occasional mitosis. There is little degeneration. Carcinoma." On account of the pathologic diagnosis of cancer, complete removal of the left lobe and the greater part of the right was carried out in a second stage. The patient made a good recovery, aside from paralysis of the left recurrent nerve. No malignancy was observed on pathologic examination of the specimen removed at the second operation.

Following discharge she had a series of X-ray treatments, and her metabolism was closely followed to give warning of the development of myxœdema. Although the rate dropped to minus 17 per cent., clinical myxœdema was not apparent. In January, 1927, a small nodule was palpated to the left of the trachea, and an X-ray of the chest showed a metastasis in the region of the right lung hilus. Further intensive X-ray treatment was carried out. In spite of this, further small nodules appeared under the scar, and the lung metastases increased slowly in size. Nevertheless, thirty-two months after operation, the patient was in good general condition, the metastases were small and apparently nearly at a standstill, not interfering with comfort.

Comment. — This case illustrates the impossibility of diagnosis in certain cases of encapsulated malignant tumors of the thyroid. The only feature which could be considered at all suggestive of carcinoma was the steadily progressive growth. It seems probable from the postoperative course that earlier operation might have led to a cure.

Case No. 5382. *Thyroid Malignancy with Acute Course*

History. — A man of 63 entered the hospital on December 13, 1927, complaining of a swelling of the neck of two weeks' duration. Previous to twelve weeks before entry, the patient felt well in every respect. About this time hoarseness developed, accompanied by a dry hacking cough. The swelling of the neck involved the thyroid region, and was bilateral from its first appearance. It increased rapidly in size for a few days and since then had appeared to diminish. There had been no pain, tenderness, or redness of the skin. He had had two attacks of dizziness with headache, and one attack of choking on swallowing solid food. He had noted no actual dyspnœa, but breathing seemed to require increased effort. His past history was negative aside from the presence of renal calculus. There had been no previous tumor of the neck or hoarseness. He worked as foreman until within three days of entry.

Examination. — This showed a muscular man with a visible tumor in the lower neck, extending across the median line, and upward under the sternomastoid muscle, somewhat larger on the left than on the right. On palpation it was hard and nodular, and firmly fixed to the deeper tissues, although the skin was movable over it. The eyes were slightly prominent, the left pupil smaller than the right, and the left eyelid slightly ptosed. There was a slight tremor of the fingers. X-ray showed no mediastinal extension. The pulse was 74, the basal metabolic rate plus 18 per cent.

Management. — The condition was considered to be malignant disease of the thyroid, probably diffuse carcinoma, by several surgical consultants, who advised against operation, and recommended X-ray treatments. The first series of exposures was completed December 24, 1927, and the patient was discharged.

He reëntered on January 19, 1928, somewhat improved in respect to cough, hoarseness and respiratory distress, but having increasing difficulty in swallowing, particularly during the past five days. The tumor apparently had not changed. On the next day a gastrostomy was done under local anæsthesia. Following this he had repeated attacks of respiratory obstruction, became comatose and died on January 24, 1928, eighteen weeks after the first symptom of hoarseness, and eight weeks after the first appearance of the tumor. Autopsy was refused.

Comment. — While the diagnosis was not established, there seems little doubt that it was malignancy of the thyroid. This case illustrates the fulminating course occasionally seen in carcinoma of the thyroid.

Case No. 288536. *Pulsating Tumor of the Clavicle of Probable Thyroid Origin*

History. — A housewife of 52 was admitted to the surgical wards on January 10, 1928, complaining of pain in the left side of the neck and shoulder. This pain developed two years before, and was brought on by working hard, especially by movements of the left arm. Benefit was obtained only by rest. Six and a half months ago following a fall the pain became constant and increasingly severe, and was located at the left sterno-clavicular articulation. Shortly afterward a tumor in this situation was noticed, which had increased slowly in size. There had been no hæmaturia or other urinary symptoms.

Examination. — This showed a somewhat obese woman having a smooth, elastic, pulsating tumor at the left sterno-clavicular articulation about 6 cm. in diameter, which seemed to arise from the clavicle, but was not

attached to the skin. The thyroid and abdomen were negative to palpation. Destruction of the inner end of the clavicle was found on X-ray examination. A pyelogram showed some deformity of the calices of the left kidney. The tumor was considered to be a metastasis from a hypernephroma in spite of the absence of urinary symptoms. Since no other metastases could be demonstrated, and an X-ray consultant stated the response of hypernephroma to radiation was usually not satisfactory, operation was undertaken.

Management. – Operation was performed on January 28, 1928 by Dr. D. F. Jones. The upper portion of the left half of the sternum, about 6 cm. of the first rib, and the inner half of the clavicle were removed, thus excising the whole tumor. The patient made a good recovery. The pathologic report by Dr. H. F. Hartwell was, "The inner end of the clavicle which is 6 cm. long has a small portion of the adjoining sternum and the first rib attached. A well-defined, soft tumor, the size of a hen's egg, measuring 4.3 cm. in greatest diameter, projects from the upper surface of the clavicle beneath the muscle. It has a pale red, firm surface on section. Section of the clavicle shows the inner end of the marrow cavity filled with soft, reddish tumor for a distance of 3 cm. from its articulation with the sternum. The tumor mass projects from the under surface of the clavicle for a short distance where it is apparently covered by a thin layer of periosteum. There is no evidence of cortical bone along the extent of the tumor. The projecting portion of the tumor above the clavicle shows no evidence of a periosteal capsule. A microscopic examination of the tumor shows a structure of small epithelial cells in small, solid columns which are separated by relatively wide blood vessels with thin walls. The tumor cells differentiate to small tubules or follicles filled with homogeneous material which looks like colloid. In many places these follicles are abundant and closely reproduce the structure of thyroid gland. They are circular and lined by single layers of cuboidal epithelium. The cells in columns are uniform in size and shape. Occasional small areas are seen where they are larger and more irregular with darker nuclei. There are few mitotic figures. From morphological evidence, it seems probable that this tumor arises from thyroid, either from thyroid gland or from aberrant groups of thyroid cells. Its structure does not suggest the usual form of hypernephroma. Metastatic adenocarcinoma, probably of thyroid origin."

Comment. — The most probable explanation of this growth is that it arose by metastases from the thyroid. Such single metastases to bone of thyroid origin are not extremely rare, and may occur in the absence of any detectable thyroid tumor.

Thyroiditis

Gross inflammatory changes in the thyroid are surprisingly infrequent and may be placed at less than one per cent. of cases of thyroid disease admitted for hospital care. Although it is obvious that the thyroid neither communicates normally with any body cavity, nor is in close relation with any structure commonly subject to septic inflammation, and also has an excellent blood supply with a free lymphatic drainage, the ultimate reason for its relative immunity from infection is obscure. The presence of adenomatous changes with secondary degenerative processes renders the thyroid more liable to infection. On this account strumitis, or inflammation of a goitre, is sometimes separated from thyroiditis occurring in a normal gland. Degenerative changes described as toxic thyroiditis may be found at autopsy in patients dying of infectious or septic diseases, but are not detectable clinically.

Types of Thyroiditis

Thyroiditis may be acute or chronic. If an acute inflammatory infection, it may or may not go on to suppuration and abscess formation. The non-suppurative type is sometimes spoken of as simple thyroiditis and occurs particularly in normal or hyperplastic glands. Nodular goitres are somewhat more prone to suppuration. Simple thyroiditis usually subsides without leaving any obvious change in the thyroid. Two types of chronic thyroiditis are recognized, the Riedel[17] type (fibrous or ligneous) and the Hashimoto[26] type (lymphadenoid). Chronic thyroiditis due to syphilis and to tuberculosis has been described, but they are so rare as to rate but little mention.

Acute Thyroiditis. — Acute thyroiditis occurs usually in early

adult life and is, as a rule, secondary to obvious infection elsewhere in the body, more particularly in the respiratory tract, although it may accompany typhoid fever, pyogenic infections, and a wide variety of infectious diseases. The disease most constantly associated with thyroiditis is Chagas fever[18, 19], an insect-borne trypanosomiasis occurring in South America. In young children it is ordinarily fatal, but in older children and adults it may assume a chronic form with associated thyroid enlargement, and may sometimes result in myxœdema. De Quervain[20], who has made a comprehensive study of non-suppurative thyroiditis, asserts that when accompanying rheumatism, malaria or measles, the affection is of the simple type, and does not proceed to suppuration. Clute and Smith[21] have recently discussed acute thyroiditis, with particular reference to the suppurative form.

Acute thyroiditis is characterized by enlargement and tenderness of the thyroid, constitutional disturbance, and pain at times radiating to the back of the neck and ear. Swallowing may be painful, and occasionally definite obstructive symptoms may develop, more particularly if there has been evidence of obstruction previous to the thyroiditis. Lahey[22] has pointed out that the chin may be held depressed, and that further depression may occur on swallowing in the effort to avoid pressure on the sensitive thyroid from the overlying muscles. Other acute inflammatory processes occurring in close relation to the thyroid may be difficult to distinguish from thyroiditis, as may the reaction following hæmorrhage into a goitre. The prognosis in simple thyroiditis is good, the process ordinarily subsiding within ten days. Treatment need only be directed toward increasing the patient's comfort, which may be accomplished by means of sedatives and an ice collar.

Suppurative Thyroiditis. — This may lead to serious complications and even death, either through mediastinitis or perforation of the trachea or œsophagus or from associated œdema and pressure. The distinction from simple thyroiditis depends chiefly on the intensity of the local signs and the constitutional reaction. On account of the depth of the thyroid, redness, heat and a sense of fluctuation are hardly to be expected. If suppuration seems probable, it is safest to expose the thyroid through a transverse incision with a view to drainage. When a single adenomatous cyst is the seat of the infection, often it may be readily enucleated, as pointed out by de Quervain[23]. With prompt and adequate treatment, the prognosis is good.

Chronic Thyroiditis. — Chronic thyroiditis as a purely histologic finding is not uncommon as an accompaniment of long standing toxic goitre. As a clinical entity it is seen as a slowly progressive disease producing chiefly pressure or hypothyroid symptoms. The two types, Riedel's and Hashimoto's, are difficult to distinguish clinically, although they are quite distinct anatomically.

Riedel's strauma is rare. Collective reviews have been published by Shaw and Smith[27] and by Smith and Clute[28]. The latter authors were able to find only thirty-five cases in the literature in 1926, to which they add five of their own. The condition, however, may be overlooked or confused with malignancy and perhaps is not so unusual as these figures suggest. It occurs in women in the proportion of 3 to 1, chiefly from the fourth decade on, and is characterized by a very slow increase in the thyroid, occasionally unilateral at first, forming a smooth or slightly nodular, symmetrical goitre of moderate size, which is neither tender nor painful but is striking in its hard consistency. The thyroid becomes firmly adherent to adjacent structures, but

not to the skin. The regional nodes usually are not enlarged. The patients are otherwise in fair health, and their basal metabolic rate is within normal limits or reduced. Obstructive symptoms are produced mechanically by the constricting action of the goitre and its adhesions and lead the patient to demand treatment. The differential diagnosis is essentially from malignancy and can not be made with certainty, although the clinical course and characteristics of the goitre may suggest the true condition. Thyroidectomy is necessary to relieve the obstructive symptoms and sense of pressure, although it may be difficult to carry out on account of surrounding adhesions. Sometimes tracheotomy becomes necessary. While myxœdema may develop after subtotal removal of a sclerosed gland, it is preferable to the obstruction caused by the goitre.

Hashimoto's form of chronic thyroiditis is chiefly important from the therapeutic angle in that it is sometimes amenable to irradiation treatment. Also, when surgery becomes necessary, Hashimoto's type is easier to deal with than Riedel's, because the infiltrating style of growth is lacking.

Tuberculosis and syphilis of the thyroid have been reported but are so rare as to be no practical problem. We have once seen a case of infection of the thyroid by monilia.

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